Syllabus

Topics in Clinical Trials

Rice University Department of Statistics STAT 630 and
University of Texas GSBS
Fall 2020

Overview

This course will provide an overview of methods for the design and analysis of clinical trials. Topics will include fundamental principles and commonly used designs for phases I, II and III trials. Advanced topics will include flaws with many conventional methods, hybrid designs, dealing with multiple outcomes, bias correction, precision medicine, and Bayesian methods.

Time: 9:30 am – 10:50 am Monday and Wednesday

Location: Zoom (https://riceuniversity.zoom.us/j/92511748259?pwd=VGZIZUp1ZHozQ0U5VEp4dnpCUWVOQT09**)**

Instructors: There are two instructors for the course. Each instructor will cover about 7 weeks of the course. Dr. Ruitao Lin will cover general topics and clinical trial designs, and Dr. Thall will cover additional topics and recently developed methods, as time permits.

Instructors:	Peter F. Thall, PhD	Ruitao Lin, PhD
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Office Hours:	By Appt	By Appt

Textbooks:

Bayesian Designs for Phase I-II Clinical Trials, Y Yuang, H Nguyen, and PF Thall. Chapman & Hall/CRC, 2016.

Clinical Trial Design: Bayesian and Frequentist Adaptive Methods, G Yin, Wiley, 2012.

Recommended Reading

Fundamentals of Clinical Trials, 4th Edition. LM Friedman, CD Furberg, DL DeMets. Springer, 2010.

Bayesian Approaches to Clinical Trials and Health-Care Evaluation, D Spiegelhalter, KR Abrams, JP Myles, Wiley, 2004.

Statistical Remedies for Medical Researchers, PF Thall, Springer Series in Pharmaceutical Statistics, 2020.

Bayesian Adaptive Methods for Clinical Trials, SM Berry, BP Carlin, JJ Lee, P Muller, CRC Press, 2010.

Homework: Each of the two major parts will include approximately 3 to 5 homework assignments. In the first part, homework assignments include derivation of statistical models or proofs of theorems, and simple R programming tasks to implement conventional trial designs. In the second part, most of the homework assignments will be construction and

detailed descriptions of clinical trial designs using existing computer software, and a very few additional assignments requiring detailed write-ups of published papers. All students are required to complete the homework assignments. Homework will be submitted at the beginning of class on the due date. If circumstances beyond the student's control arise and an assignment cannot be submitted on the due date, an instructor should be contacted prior to the due date. With an instructor's permission, late homework may be accepted within one week of the due date. All decisions will be made on an individual student basis and the final decision rests with the instructor assigning the homework.

Website: https://canvas.rice.edu/courses/33819

Software Download sites https://biostatistics.mdanderson.org/SoftwareDownload

https://trialdesign.org

Course Grade The final grade will be determined by the homework scores.

Absence Policies Class attendance is required but not explicitly graded. Only university excused absences will be accepted for missing homework or exams. Documentation will be required. If you know you will miss an exam for a valid reason, please see or email me as soon as possible. Unexcused absences will be considered on a case–by-case basis.

Rice Honor Code In this course, all students will be held to the standards of the Rice Honor Code, a code that you pledged to honor when you matriculated at this institution. If you are unfamiliar with the details of this code and how it is administered, you should consult the Honor System Handbook at http://honor.rice.edu/honor-system-handbook/. This handbook outlines the University's expectations for the integrity of your academic work, the procedures for resolving alleged violations of those expectations, and the rights and responsibilities of students and faculty members throughout the process.

Disability Resource Center If you have a documented disability or other condition that may affect academic performance you should: 1) make sure this documentation is on file with the Disability Resource Center (Allen Center, Room 111 / adarice@rice.edu / x5841) to determine the accommodations you need; and 2) talk with me to discuss your accommodation needs.

Syllabus Change Policy This syllabus is only a guide for the course and is subject to change with advanced notice.

Other policies: All other policies of Rice University are observed: see http://ga.rice.edu/; All other policies of UTHealth GSBS are observed: see https://gsbs.uth.edu/

Lecture Topics

The topics listed below will be covered as time permits

Lecture Topics for Dr. Lin

1. Fundamentals of Clinical Trials
    a. Brief introduction on clinical trials
    b. Phase I-IV of clinical trials
    c. Basic Bayesian statistics
        i. Bayes' theorem
        ii. Typical examples
        iii. Bayes factors
2. Phase I Clinical Trials
    a. Overview of phase I clinical trials
    b. 3+3 design
    c. Biased coin dose-finding method
    d. Continual reassessment method
    e. Bayesian model averaging continual reassessment method
    f. Model assisted designs using Bayesian decision theory
3. Phase II Clinical Trials
    a. Overview of phase II clinical trials
    b. Simon's two-stage design
    c. Bayesian monitoring with posterior probability
    d. Bayesian monitoring with predictive probability
4. Phase III Clinical Trials
    a. Overview of phase III clinical trials
    b. Power and sample size calculation
    c. Group sequential design
        i. Multiple testing procedure
        ii. Pocock's design
        iii. O'Brien and Fleming's design
        iv. Stopping boundary computation
        v. Sample size calculation for group sequential design
    d. Sample size re-estimation
        i. Fisher's combination criterion
        ii. Conditional power approach
    e. Adaptive randomization

Lecture Topics for Dr. Thall

1. Issues with the conventional three-phase paradigm
    a. Toxicity-only dose finding: Three common problems
    b. Expansion cohorts
    c. Practical sample size computation
        a. The two stage size-power algorithm
        b. Using the algorithm backwards
        c. Computing sample size based on parameter estimation
    d. Knocking Down the Straw Man: Issues with the Simon design

    e. Monitoring event times in phase II
2. Designs with multiple outcomes
    a. Dirichlet-multinomial model-based phase II design
    b. Bivariate binary outcomes: The EffTox design
    c. Phase I-II designs for 3 to 5 outcomes
    d. Dimension reduction and loss of information
    e. Go/No-Go decisions for phase III: The (response, survival) mixture problem
3. Randomization and bias
    a. Simpson's Paradox
    b. Single-arm trials and biased estimation
    c. A Bayesian rationale for randomization
    d. The "exploration-versus-exploitation" problem
    e. Adaptive randomization in comparative trials: Two simulation studies
4. Bias correction methods
    a. Pair matching
    b. Inverse probability of treatment weighting
    c. Bayesian nonparametric regression
5. Misuse of p-values
    a. Significant tests with tiny estimated effects
    b. Insignificant tests with large estimated effects
    c. The three ways that p-values may be misinterpreted or misused
        a. To quantify strength of evidence
        b. To make dichotomous decisions
        c. Misinterpreting p-values
    d. A "p-value free" Bayesian paradigm for regression analysis
6. Precision Medicine
    a. Natural Killer cell dose finding: Using 5 time-to-event outcomes
    b. SubTiTE: Dose finding with collapsing subgroups
    c. A Randomized trial design for ordinal outcomes with 2 subgroups
    d. Adaptive enrichment design
    e. Bayesian nonparametric regression for precision dosing in stem cell transplantation
7. A new phase I-II-III design paradigm

Lecture Schedule

Week	Date	Topic	Readings*	Notes	Instructor
1	Aug-24-M	**Introduction**	CTD ch1-3	Overview of the course	Lin
	Aug-26-W	**Bayesian inference**	CTD ch1-3	Clinical trials and Bayesian statistics	Lin
2	Aug-31-M	**Phase III trials**	CTD ch6	Power and sample size	Lin
	Sep-2-W			Continuous endpoints	Lin
3	Sep-	Labor Day	No class	No class	No class

	7-M				
	Sep-9-W			Binary and survival endpoints Multiple testing	Lin
4	Sep-14-M			Group sequential design I	Lin
	Sep-16-W			Group sequential design II	Lin
5	Sep-21-M			Sample size re-estimation	Lin
	Sep-23-W	**Phase I trials**	CTD ch4	Introduction and 3+3 design	Lin
6	Sep-28-M			CRM and BMA-CRM	Lin
	Sep-30-W			Model assisted designs	Lin
7	Oct-5-M	**Phase II trials**	CTD ch5	Simon's II stage design	Lin
	Oct-7-W			Posterior/predictive monitoring	Lin
8	Oct-12-M			Phase I/II trials	Lin
	Oct-14-W	Flaws with conventional paradigms		Misuse of p-values, strength of evidence, the phase II → phase III problem	Thall
9	Oct-19-M	Flaws with conventional paradigms		planned confounding, stratification, Unsafe safety rules, Simpson's Paradox	Thall
	Oct-21-W	Flaws with conventional paradigms		Confounding, magic biomarkers, causation and lurking variables, phase II-III designs	Thall
10	Oct-26-M	Phase II trials		Phase II with multiple outcomes	Thall
	Oct-28-W	Phase II trials		Phase II with event times	Thall
11	Nov-2-M	Phase I-II trials		The EffTox Design for phase I-II	Thall
	Nov-4-W	Flipping coins for fair comparisons		Randomization and bias	Thall

12	Nov-9-M	Comparisons from observational data		Bias correction methods	Thall
	Nov-11-W	Adaptive randomization in comparative trials		Problems with adaptive randomization	Thall
13	Nov-16-M	Precision phase I trials		Sub-TiTe design for phase I : Collapsing subgroups	Thall
	Nov-18-W	Precision phase I-II trials		Cell dose optimization: Five event times	Thall
14	Nov-23-M	Precision phase III trials		Randomized trials with subgroups	Thall
	Nov-25-W	Thanksgiving holidays	No class	No class	No class
15	Nov-30-M	Bayesian nonparametric survival analysis for precision medicine		Precision dosing in stem cell transplant	Thall
	Dec-2-W	A new all-In-one paradigm: Crushing the conventional approach		The phase I-II-III design	Thall