Clinical Trials

Yu Shyr

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Textbook


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1 Design and Conduct

The theoretical and practical challenges to be considered in designing and conducting a clinical trial will be presented. Topics to be discussed include the specification of a primary objective, adherence to accepted ethical guidelines, the role of randomization and the means of its implementation, the type and assessment of blinding, the choice of design strategy and design-strengthening features, and the considerations involved in sample size determination and patient recruitment.

2 Analysis of Clinical Trials

Methods of analysis appropriate to various designs, such as up-and-down design, titration design, Bayesian design, randomized controlled studies, crossover designs, factorial designs, group allocation designs, hybrid designs, and designs for non-inferiority study, will be presented. The statistical approach will be based on empirical use of methodologies rather than formal algebraic knowledge, the emphasis on understanding what the procedures do and applications to data analysis. Methods of data collection, monitoring response variables, and data quality control will be discussed.

3 Topics

All classes meet 8:30 – 11:00 except 11/17 (9:00 – 11:00).

Classes meet in 206 Preston Research Building except 11/19 (MCN C2209).
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<thead>
<tr>
<th>Week 1</th>
<th>Topic</th>
<th>Reading</th>
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<tr>
<td>Monday, 11/3</td>
<td>FDA case study</td>
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<td>Chapter 1</td>
<td>Overview of clinical trials</td>
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<td>Tuesday, 11/4</td>
<td>Experiment design I</td>
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<td>Chapter 2</td>
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<td>Wednesday, 11/5</td>
<td>Experiment design I/II</td>
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<tr>
<td>Thursday, 11/6</td>
<td>Experiment design II</td>
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<td>Friday, 11/7</td>
<td>Guest speaker: Michael DeBaun</td>
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<tr>
<td>Chapter 4</td>
<td>“Conducting pilot and feasibility trials: the initial step”</td>
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<td>Week 2</td>
<td>Topic</td>
<td>Reading</td>
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<tr>
<td>Monday, 11/10</td>
<td>Randomization &amp; Blinding</td>
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<td>Sample size determination</td>
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<td>Chapter 6</td>
<td><strong>Homework 1 due</strong></td>
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<td>Wednesday, 11/12</td>
<td>Monitoring trial progress</td>
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<td>Chapter 7</td>
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<td>Thursday, 11/13</td>
<td>Baseline assessment, subgroup analysis, subject recruitment, multicenter trials</td>
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<td>Chapter 8/9</td>
<td>Statistical approaches for various endpoints (statistical analysis I)</td>
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<tr>
<td>Friday, 11/14</td>
<td>Statistical approaches for various endpoints (statistical analysis II)</td>
<td>14, 16, 18</td>
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<td>Chapter 10</td>
<td><strong>Homework 2 due</strong></td>
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<td>Chapter 11</td>
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<tr>
<td>Tuesday, 11/18</td>
<td>Non-inferiority, data collection, trial closeout, intent-to-treat Homework 3 due</td>
<td>10 – 11, 16</td>
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<td>Wednesday, 11/19</td>
<td>Meta-analysis Final review</td>
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<td>MCN C2209</td>
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<tr>
<td>Thursday, 11/20</td>
<td>Presentations: Students will critique recently published clinical trials Report due Dec. 3</td>
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### 4 Goals

#### Chapter 1

**FDA case study**

**Overview of clinical trials**

- What is a clinical trial?
- Issues in modern clinical trials
- Formulating research questions
- Study population
Chapter 2

Phase I trials
- Up-and-down design
- Single patient per cohort design
- Titration design

Phase II trials
- Randomized dose ranging design
- Randomized titration design
- Two-stage phase II designs
- Multistage design
- Bayesian design
- Randomized phase II design
- Multiple outcomes design

Chapter 3

Phase III trials
- Randomized controlled clinical trials
- Uncontrolled clinical trials
- Historical controls
- Crossover designs
- Withdrawal studies
- Factorial designs
- Group allocation designs
- Studies of equivalency

Ethical issues

Chapter 4

Guest Lecture: Michael DeBaun
- Conducting pilot and feasibility trials: the initial step
Chapter 5

Randomization methods

- Simple randomization
- Replacement randomization
- Random permuted blocks
- Biased coin

Other randomization methods

Blinded studies

Chapter 6

Sample size determination

- Dichotomous response variables (independent, paired)
- Continuous response variables (independent, paired)
- Time to failure

Chapter 7

Monitoring trial progress

- Reasons for interim monitoring
- Repeated testing for significance
- Decision for early termination
- Decision for extending a trial
- Techniques for repeated testing

Chapter 8

Baseline assessment, subgroup analysis, recruitment, multicenter trials

- Use of baseline data
- Analysis of baseline comparability
• Balance and imbalance
• Difficulties of subgroup analysis
• Recruitment of study subjects
• Multicenter trials

Chapter 9

Statistical analysis I

• Statistical approach for various experimental designs
• Key concepts for statistical analysis
• Statistical approaches for various endpoints: t-test, chi-square test, Fisher’s exact test, analysis of variance, regression analysis, longitudinal analysis, nonparametric statistics
• Logistic regression model

Chapter 10

Statistical analysis II

• Statistical approaches for crossover and factorial designs
• Estimation and comparison of survival curves
• Cox proportional hazards model
• Analysis of covariance (ANCOVA)
• Multivariate analysis
• Multiple comparisons
• Missing data analysis

Chapter 11

Guest Lecture: Wayne Ray

• U.S. Drug Regulatory System
Chapter 12

Non-inferiority, data collection, trial closeout, intent-to-treat

• Non-inferiority trials
• Statistical methods for non-inferiority analysis
• Data collection and quality control
• Trial closeout procedures
• Intent-to-treat

Chapter 13

Meta-Analysis

• Overview
• Meta-analysis vs. randomized clinical trials
• General and statistical considerations
• Assessing trial heterogeneity
• Meta-analysis software
• Examples of meta-analysis

5 Other References


### 6 Software

**PS Sample Size and Power Calculations** (developed by William Dupont, free download)

**PASS 12** Power analysis and sample size program

**EaST 5.4** Software for design and interim monitoring of group sequential clinical trials

**nQuery Advisor + nTerim 2.0** Sample size and power determination

**Microsoft Access**

### 7 Grade

- Homework 30%
- Presentation 40%
- Final report 30%