**COURSE CONTENT FOR MH4512**

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| **Academic Year** | 1819 | **Semester** | 2 |
| **Course Coordinator** | Yeo Kwee Poo | | |
| **Course Code** | MH4512 | | |
| **Course Title** | Clinical Trials | | |
| **Pre-requisites** | MH3500 Statistics and MH3510 Regression Analysis | | |
| **No of AUs** | 4 AU | | |
| **Contact Hours** | 3 hours lecture and 1 hour tutorial per week | | |
| **Proposal Date** | 26-Apr-2018 | | |

**Course Aims**

Clinical trials are used to evaluate the safety, efficacy and feasibility of a treatment or a drug in human. It is a critical step in commercialising any pharmaceutical products. This course focuses on the statistical aspects of conducting clinical trials. We will introduce drug development process, best practices and regulatory requirements in the industry. Various trial designs and analysis methods at different phases of drug development will be discussed. This course is essential for students who plan to work with clinical or medical data. You will acquire knowledge in analysing clinical data and in interpreting the analysis results. You will also learn to appreciate medical research papers.

**Intended Learning Outcomes (ILO)**

By the end of the course, students should be able to:

1. Recognise the importance of clinical trials in pharmaceutical industry.
2. Associate study design with relevant regulations, guidelines and best practices.
3. Apply the mixed effects model to analyse data with repeated measures.
4. Perform statistical testing according to the primary objectives of clinical studies.
5. Interpret and articulate the relevance of statistical results to clinical outcomes.
6. Critique the statistical principles in medical research papers.
7. Determine the sample size required under given conditions.

**Course Content**

General Introduction to Clinical Trials

- Definition of clinical trials
- Regulatory requirements and guidelines
- Good clinical practice
- Drug development process
- Phases of clinical trials

Mixed Effects Model

- Fixed and random effects
- Crossover design, period and sequence effects of a trial
- Repeated measures and effects of missing data
- Total, Inter- and intra-subject variances
- Using SAS's Proc Mixed procedure
- Variance and covariance structures

Basic Pharmacokinetics

- Pharmacokinetic and Pharmacodynamic
- Absorption, Distribution, Metabolism and Elimination of drugs
- Pharmacokinetic parameters and their estimation methods
- Log-transformation, log-normal distribution and coefficient of variation

Treatment Comparison in Various Designs

- Bioequivalence, Superiority, and non-inferiority trials
- Two one-sided tests

- Equivalence and non-inferiority margins
- Dose proportionality study, confidence interval approach
- Food effects, hepatic or renal impairment, age or Gender comparisons
- Drug-Drug interaction trials

Nonparametric Methods
- Sign test for median
- Wilcoxon signed-rank test
- Wilcoxon rank sum test
- Confidence interval for median and difference of medians

Longitudinal Data Analysis
- Characteristics of Longitudinal Data
- Change from baseline analysis
- Analysis of covariance approach
- Mixed effects approach with various covariance structures

Sample Size and Power Calculations
- Clinically meaningful difference and primary study endpoint
- Sample size estimation and power calculation for bioequivalence, superiority and non-inferiority trials

**Assessment (includes both continuous and summative assessment)**

| Component | Course ILO Tested | Related Programme LO or Graduate Attributes | Weighting | Team/Individual | Assessment rubrics |
|---|---|---|---|---|---|
| 1. Final Examination | 2 – 7 | A1, A2, A3, B1, B2, C1 | 60% | Individual | Appendix 1 |
| 2. Group Presentation | 1 – 6 | A1, A2, B1, B2, B3, C1, C2, D, E | 30% | Team | Appendix 2 |
| 3. Assignments | 2 – 5, 7 | A1, A2, A3, A4, B1, B2, B3, B4, C1 | 10% | Individual | Appendix 1 |
| Total | | | 100% | | |

*Graduates of MAS programmes should be able to:*

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| *Competence* | |
| *A1: {Understanding}* | *independently process and interpret mathematical theories and methodologies, and apply them to solve problems* |
| *A2: {Rigour}* | *formulate mathematical statements precisely using rigorous mathematical language* |
| *A3: {Intuition}* | *discover patterns by abstraction from examples* |
| *A4: {Modern Tool Usage}* | *use computer technology to solve problems, and to communicate mathematical ideas* |
| *Creativity* | |
| *B1: {Critical Thinking}* | *critically assess the applicability of mathematical tools in the workplace* |
| *B2: {Analysis}* | *critically analyse data from a multitude of sources* |

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| *B3: {Interdisciplinarity}* | *build on the connection between subfields of mathematics to tackle new problems* |
| *B4: {Creativity}* | *develop new applications of existing techniques* |
| *Communication* | |
| *C1: {Communication}* | *present mathematics ideas logically and coherently at the appropriate level for the intended audience* |
| *C2: {Teamwork}* | *work in teams on complicated projects that require applications of mathematics, and communicate the results verbally and in written form* |
| *Civic-Mindedness* | |
| *D: {Professionalism}* | *develop and communicate mathematical ideas and concepts relevant in everyday life for the benefits of society* |
| *Character* | |
| *E: {Ethics}* | *act in socially responsible and ethical ways in line with the societal expectations of a mathematics professional, particularly in relation to analysis of data, computer security, numerical computations and algorithms* |

**Formative feedback**

Component 2: Feedback on presentation skills, understand of statistical as well as medical interpretations of research papers.

Component 3: You will receive individual written and/or verbal feedback about your assignments, as the lecturer will return each assignment individually.

**Learning and Teaching approach**

| **Approach** | **How does this approach support students in achieving the learning outcomes?** |
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| Lecture | Help you understand the motivation and definitions of the concepts and notions, approaches to solving problems in pursuant to learning outcomes |
| Presentation | Develop presentation skills, team work and professionalism |
| Assignment | Develop writing and presentation skills, strengthen the understanding of the concepts and notions, and apply the techniques in problem solving |
| Tutorial | Develop problem solving skills, reinforce the understanding of the concepts and notions |

**Reading and References**


1. *Clinical Trial Data Analysis Using R and SAS* (2nd Edition). Ding-Geng Chen, Karl E Peace and Pinggao Zhang. Chapman & Hall, CRC Press (2017), 978-1498779524
2. *Design and Analysis of Clinical Trials: Concepts and Methodologies.* Shein-Chung Chow and Jen-Pei Liu. Wiley (2014), 978-0470887653
3. *Introduction to Statistical Methods for Clinical Trials.* Thomas D Cook and David L DeMets. Chapman & Hall, CRC Press (2008), 978-1584880271
4. *Applied Mixed Models in Medicine (2nd Edition).* Helen Brown and Robin Prescott. Wiley (2006), 978-0470023563
5. *Longitudinal Data analysis.* Donald Hedeker and Robert D Gibbons. Wiley (2006), 978-0471420279


**Course Policies and Student Responsibilities**

(1) General

Students are expected to complete all assignments and participate in the group presentation. Students are expected to take responsibility to follow up with course notes, assignments and course related announcements if they are absent.

(2) Absenteeism

Absence from presentation sessions and examination without a valid reason will affect your overall course grade. Valid reasons include falling sick supported by a medical certificate and participation in NTU's approved activities supported by an excuse letter from the relevant bodies.

(3) Absence Due to Medical or Other Reasons

If you are sick and not able to attend the presentation sessions, you have to submit the original Medical Certificate (or another relevant document) to the administration to obtain official leave. In this case, the missed assessment component will not be counted towards the final grade.

**Academic Integrity**

Good academic work depends on honesty and ethical behaviour. The quality of your work as a student relies on adhering to the principles of academic integrity and to the NTU Honour Code, a set of values shared by the whole university community. Truth, Trust and Justice are at the core of NTU's shared values.

As a student, it is important that you recognize your responsibilities in understanding and applying the principles of academic integrity in all the work you do at NTU. Not knowing what is involved in maintaining academic integrity does not excuse academic dishonesty. You need to actively equip yourself with strategies to avoid all forms of academic dishonesty, including plagiarism, academic fraud, collusion and cheating. If you are uncertain of the definitions of any of these terms, you should go to the academic integrity website for more information. Consult your instructor(s) if you need any clarification about the requirements of academic integrity in the course.

Use of materials outside the course is strongly discouraged. If you use outside source, you must reference it in your solution.

You must write up your solutions by yourself and understand anything that you hand in.

**Course Instructors**

| Instructor | Office Location | Phone | Email |
|---|---|---|---|
| Yeo Kwee Poo | SPMS-MAS-04-16 | 6513-7456 | kweepoo@ntu.edu.sg |

**Planned Weekly Schedule**

| Week | Topic | Course ILO | Readings/ Activities |
|---|---|---|---|
| 1 | General Introduction to Clinical Trials | 1, 2 | Lecture notes |
| 2 – 4 | Mixed Effects Model | 3 | Lecture notes / Tutorial / Assignment |
| 5 | Basic Pharmacokinetics | 2, 4 | Lecture notes / Tutorial / Assignment |
| 6 – 8 | Treatment comparison in Various Designs | 3 – 5 | Lecture notes / Tutorial / Assignment |
| 9 – 10 | Nonparametric Methods | 3 – 5 | Lecture notes / Tutorial / Assignment |

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| 11 | Longitudinal Data Analysis | 3 – 5 | Lecture notes / Tutorial / Assignment |
| 12 – 13 | Sample Size and Power Calculations | 7 | Lecture notes / Tutorial / Assignment |

**Appendix 1: Assessment Criteria for Assignments and Final Exams**

These assessment tasks are meant to assess your ability to:

1. Associate study design with relevant regulations, guidelines and best practices.
2. Apply the mixed effects model to analyse data with repeated measures.
3. Perform statistical testing according to the primary objectives of clinical studies.
4. Interpret and articulate the relevance of statistical results to clinical outcomes.
5. Critique the statistical principles in medical research papers.
6. Determine the sample size required under given conditions.

| **Criteria** | **Standards** | | |
|---|---|---|---|
| | **Fail standard** | **Pass standard** | **High standard** |
| Methods of approach (LO 2, 3, 4, 7) | • Using methods that are irrelevant or do not apply to the given problem.<br>• Invoking theorems whose conditions are not satisfied. | • Using relevant methods that help solve the problem.<br>• Invoking theorems whose conditions are satisfied. | Finding methods and utilizing theorems that are both relevant and effective |
| Validity of reasoning (LO 4, 5, 6) | Reasoning is logically invalid. | Reasoning is logically valid. | Reasoning is logically valid and effective. |
| Clarity of argument (LO 4, 5, 6) | Reasoning is poorly explained or not explained at all. | Reasoning is clear but may contain some gaps. | Reasoning is clear, precise with no or insignificant gaps. |

**Appendix 2: Assessment Criteria for Group Presentation**

This assessment task is meant to assess your ability to:

1. Recognise the importance of clinical trials in pharmaceutical industry.
2. Associate study design with relevant regulations, guidelines and best practices.
3. Apply the mixed effects model to analyse data with repeated measures.
4. Perform statistical testing according to the primary objectives of clinical studies.
5. Interpret and articulate the relevance of statistical results to clinical outcomes.
6. Critique the statistical principles in medical research papers.

| **Criteria** | **Standards** | | |
|---|---|---|---|
| | **Fail standard** | **Pass standard** | **High standard** |
| Methods of approach (LO 1, 2, 3, 6) | • Abstracting irrelevant information or do not mention the clinical objectives.<br>• Wrongly explain the concepts or objectives of the presentation paper. | • Using relevant information that helps explain the clinical objectives.<br>• Correctly identify and explain the objectives and methods of the paper. | Obtaining additional information that are both relevant and effective to explain the clinical objectives. |
| Validity of reasoning (LO 4, 5, 6) | Reasoning and illustration are logically invalid. | Reasoning and illustration are logically valid. | Reasoning and illustration are logically valid and effective. |
| Clarity of argument (LO 4, 5, 6) | Reasoning is poorly explained or not explained at all. | Reasoning is clear but may contain some gaps. | Reasoning is clear, precise with no or insignificant gaps. |