



Course guide

200628 - DAIC - Advanced Experimental Design in Clinical Research

Last modified: 02/06/2017

Unit in charge: School of Mathematics and Statistics
Teaching unit: 1004 - UB - (ENG)Universitat de Barcelona.
Degree: MASTER'S DEGREE IN STATISTICS AND OPERATIONS RESEARCH (Syllabus 2013). (Optional subject).
Academic year: 2017 **ECTS Credits:** 5.0 **Languages:** Spanish

LECTURER

Coordinating lecturer: JOSEP LLUÍS CARRASCO JORDAN

Others: Segon quadrimestre:
MIQUEL CALVO LLORCA - A
JOSEP LLUÍS CARRASCO JORDAN - A
ANTONIO MONLEON GETINO - A

REQUIREMENTS

- It is necessary that students have basic knowledge of R. In the following link the materials from a course to introduction to R are available

<http://www.ub.edu/stat/docencia/EADB/Curso%20basico%20de%20R.htm>

- It is recommended that students have taken a course in Design of Experiments or have basic knowledge on this subject. In particular it is recommended that students know the methodology outlined in chapters 12 and 13 included in Montgomery, DC (2001). Design and analysis of experiments, 5th edition. John Wiley & sons.

DEGREE COMPETENCES TO WHICH THE SUBJECT CONTRIBUTES

Specific:

5. CE-1. Ability to design and manage the collection of information and coding, handling, storing and processing it.
6. CE-2. Ability to master the proper terminology in a field that is necessary to apply statistical or operations research models and methods to solve real problems.
7. CE-3. Ability to formulate, analyze and validate models applicable to practical problems. Ability to select the method and / or statistical or operations research technique more appropriate to apply this model to the situation or problem.
8. CE-4. Ability to use different inference procedures to answer questions, identifying the properties of different estimation methods and their advantages and disadvantages, tailored to a specific situation and a specific context.
9. CE-5. Ability to formulate and solve real problems of decision-making in different application areas being able to choose the statistical method and the optimization algorithm more suitable in every occasion.
Translate to english
10. CE-6. Ability to use appropriate software to perform the necessary calculations in solving a problem.
11. CE-7. Ability to understand statistical and operations research papers of an advanced level. Know the research procedures for both the production of new knowledge and its transmission.
12. CE-8. Ability to discuss the validity, scope and relevance of these solutions and be able to present and defend their conclusions.
13. CE-9. Ability to implement statistical and operations research algorithms.

Transversal:

1. **ENTREPRENEURSHIP AND INNOVATION:** Being aware of and understanding how companies are organised and the principles that govern their activity, and being able to understand employment regulations and the relationships between planning, industrial and commercial strategies, quality and profit.
2. **SUSTAINABILITY AND SOCIAL COMMITMENT:** Being aware of and understanding the complexity of the economic and social phenomena typical of a welfare society, and being able to relate social welfare to globalisation and sustainability and to use technique, technology, economics and sustainability in a balanced and compatible manner.
3. **TEAMWORK:** Being able to work in an interdisciplinary team, whether as a member or as a leader, with the aim of contributing to projects pragmatically and responsibly and making commitments in view of the resources that are available.
4. **EFFECTIVE USE OF INFORMATION RESOURCES:** Managing the acquisition, structuring, analysis and display of data and information in the chosen area of specialisation and critically assessing the results obtained.

TEACHING METHODOLOGY

The in-person lessons consist of sessions in the classroom where the theoretical concepts are introduced with practical examples by means of slides that will be available for students.

Furthermore, the appropriate software to carry out the analyses and procedures will be also introduced by solving real data examples.

LEARNING OBJECTIVES OF THE SUBJECT

To face concrete situation, the student have to know how identifying the appropriate designs, properly carry out the experimentation and analyzing the results.

To obtain theoretical and practical knowledge of some critical designs in Biostatistics.

To know the regulatory that rules the approval of generic drugs and formulations.

To know to differentiate between a situation that requires an analysis of differences from an analysis of equivalence.

To provide the concepts and approaches to carry out an analysis of bioequivalences and equivalence in general.

To provide the concepts and approaches to carry out an analysis of concordance among measurements.

To know differentiating an analysis of concordance from an association or parameter comparison analysis.

To identify the sources of disagreement.

To provide the skill of discriminating among approaches depending of the type of data and objectives.

STUDY LOAD

| Type | Hours | Percentage |
|-------------------|-------|------------|
| Hours small group | 15,0 | 12.00 |
| Hours large group | 30,0 | 24.00 |
| Self study | 80,0 | 64.00 |

Total learning time: 125 h



CONTENTS

BLOCK 1. HIERARCHICAL FACTOR MODELS, REPEATED MEASURES AND CROSS-OVER DESIGNS

Description:

- 1.1.1. Factor designs with random effects. Mixed effects designs.
- 1.1.2. Hierarchical designs with two and three factors. Bennett-Franklin algorithm.
- 1.1.3. Repeated measures designs. Sphericity concept and ANOVA table corrections.
- 1.1.4. Crossover design concept. 2x2 crossover design (AB/BA). Crossover design of superior order and its analysis.

Full-or-part-time: 31h 15m

Practical classes: 12h

Guided activities: 8h

Self study : 11h 15m

BLOCK 2. BIOEQUIVALENCE

Description:

- 2.1. Introduction
 - 2.1.1. Bioavailability. The concept of bioequivalence between drugs. Regulatory norms.
 - 2.1.2. TOST. The principle of confidence intervals inclusion. Confidence intervals for BE. Bayesian approach. Nonparametric approach.
 - 2.1.3. The problem of residual effects (carryover)
- 2.2. Individual and multivariate Bioequivalence
 - 2.2.1. Individual and populational bioequivalence
 - 2.2.2. Multivariate bioequivalence.
- 2.3. Equivalence tests.
 - 2.3.1. General concept of equivalence test
 - 2.3.2. Main applications: goodness of fit, homogeneity of variances, additivity in linear models, equivalence of proportions
 - 2.3.3. Accessories: No inferiority testing method based on statistics and distances; bioinformatics applications

Full-or-part-time: 31h 15m

Practical classes: 12h

Guided activities: 8h

Self study : 11h 15m



BLOCK 3. ASSESSMENT OF THE DATA QUALITY: RELIABILITY AND CONCORDANCE OF MEASUREMENTS

Description:

3.1. INTRODUCTION

- 3.1.1. Model of measurement. Types of measurement errors.
- 3.1.2. Concepts: validity, accuracy, reliability and calibration.
- 3.1.3. Classification of the approaches to evaluate agreement.

3.2. ANALYSIS WITH QUALITATIVE DATA

- 3.2.1. Components of discordance: bias and association. Comparison of paired proportions. Evaluation of linear association in contingency tables.
- 3.2.2. Concordance index: kappa index and weighted kappa γ kappa. Kappa index extended to k observers.

3.3. ANALYSIS WITH CONTINUOUS DATA

- 3.3.1. Components of discordance: bias, association and heteroscedasticity.
- 3.3.2. Coefficient of concordance: definition and generalization.
- 3.3.3. Intraclass correlation coefficient: reliability, consistency and concordance.
- 3.3.4. Procedures based on probability criteria: tolerance intervals and total deviation index. Bland-Altman approach. Other approaches to assess concordance.
- 3.3.5. Assessment of individual bioequivalence as a concordance among measurements issue.

Full-or-part-time: 62h 30m

Theory classes: 22h 30m

Practical classes: 24h

Guided activities: 16h

GRADING SYSTEM

Overall mark will be obtained as an average of:

- 1) Proposed exercises (50%)
- 2) Test about theoretical concepts treated along the course (50%)

BIBLIOGRAPHY

Basic:

- Vonesh, E.F., Chinchilli, V.M. Linear and nonlinear models for the analysis of repeated measurements. Marcel Dekker, 1997. ISBN 0824782488.
- Chow, S-C., Liu, J-P. Design and analysis of bioavailability and bioequivalence studies. 3th ed. CRC, 2009. ISBN 0-8274-7572-4.
- Shoukri, M.M. Measures of interobserver agreement. Chapman & Hall/CRC, 2004.
- Agresti, A. Categorical data analysis. 2nd ed. John Wiley & Sons, Inc., 2002.
- Fleiss, J.L. Design and analysis of clinical experiments. John Wiley & Sons, Inc., 1986.

Complementary:

- Raghavarao, D.; Padgett, L.V. Block designs. analysis, combinatorics and applications. World Scientific. Series on Applied Mathematics, vol. 17., 2005. ISBN 981-256-360-1.
- Senn, S. Cross-over trials in clinical research. 2nd ed. John Wiley & Sons, Inc., 2002.
- Patterson, S., Jones, B. Bioequivalence and Statistics in Clinical Pharmacology. Chapman & Hall/CRC, 2006. ISBN 978-1-58488-530-6.
- Wellek, S. Testing statistical hypotheses of equivalence. Chapman & Hall/CRC, 2003. ISBN 1-58488-160-7.
- Dunn, G. Design and analysis of reliability studies. Oxford University Press, 1989.