200627 - AC - Clinical Trials

Coordinating unit: 200 - FME - School of Mathematics and Statistics
Teaching unit: 715 - EIO - Department of Statistics and Operations Research
1004 - UB - (ENG)Universitat de Barcelona

Academic year: 2018
Degree: MASTER'S DEGREE IN STATISTICS AND OPERATIONS RESEARCH (Syllabus 2013). (Teaching unit Optional)
ECTS credits: 5
Teaching languages: English

Teaching staff
Coordinator: ERIK COBO VALERI
Others: Primer quadrimestre:
ERIK COBO VALERI - A
ALBERTO COBOS CARBO - A
JOSÉ ANTONIO GONZÁLEZ ALASTRUE - A

Opening hours
Timetable: Please, contact by email

Prior skills
The student is expected to have some basic knowledge on descriptive statistics and statistical inference (estimation and testing), including the following: frequency tables and contingency tables; descriptive statistics for continuous variables; histograms, boxplots and scatterplots; interpretation of p-values and confidence intervals, and concepts such as statistic, parameter, and confidence level; one- and two-sided tests, null and alternative hypotheses, significance level, power, and sample size; t-tests on means; classic non-parametric tests for location (Mann-Whitney Wilcoxon rank sum and signed rank tests); z-tests on proportions and independence chi-square test; measures of effect such as difference of means and difference and ratio of proportions.
For example, the student is expected to be able to compute the variance of the difference of 2 random variables; the CI95% and the p-value for the means difference of two normally distributed independent random variables; as well as for the difference of 2 proportions from dichotomic outcomes.
The student is also expected to have some familiarity with a statistical package, preferably R. Although not strictly required, it would also be helpful to have some further knowledge about:
- Interpretation of hypotheses and P values within the Fisher evidence framework, as well as the distinction between the hypotheses to be tested and the required assumptions (see http://en.wikipedia.org/wiki/P-value)
- The concepts of alpha, beta, power Null and Alternative hypotheses within the Neyman-Pearson framework (see http://en.wikipedia.org/wiki/Type_I_and_Type_II_Errors)
- The intraclass correlation coefficient (http://en.wikipedia.org/wiki/Intraclass_correlation)
- The concept of collinearity (http://en.wikipedia.org/wiki/Collinearity#Usage_in_statistics_and_econometrics)

Requirements
Basics of experimental design, inference and R.
200627 - AC - Clinical Trials

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.
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 course is highly practical and PBL (project/problems based learning) oriented.

Teacher explanations with slides and seminar activities represents around 60% of face-to-face time. Student presentations (PBL1) of both problems and simulations, and paper reviews, 30%; and active learning activities 10% (PBL2).

Homework guided activities includes solving questionnaires, short data analyses and practical application of guidelines to selected cases.

Learning objectives of the subject

After the course, the student will be aware than only a randomized study provides the rationale to confirm and to estimate the effects of an allocated cause. The student will be able to argument and to show that the CT provides a formal basis for evidence in drug and device development; and will apply the rules to provide transparency in reporting.
# Study load

<table>
<thead>
<tr>
<th><strong>Total learning time:</strong> 125h</th>
<th>Hours large group:</th>
<th>30h</th>
<th>24.00%</th>
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<tbody>
<tr>
<td></td>
<td>Hours medium group:</td>
<td>0h</td>
<td>0.00%</td>
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<tr>
<td></td>
<td>Hours small group:</td>
<td>15h</td>
<td>12.00%</td>
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<td></td>
<td>Guided activities:</td>
<td>0h</td>
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<tr>
<td></td>
<td>Self study:</td>
<td>80h</td>
<td>64.00%</td>
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# 200627 - AC - Clinical Trials

## Content

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th><strong>Learning time:</strong> 0h 45m</th>
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</thead>
<tbody>
<tr>
<td><strong>Description:</strong></td>
<td>Theory classes: 0h 45m</td>
</tr>
<tr>
<td>Development phases. Primary and secondary objectives. Adverse events and adverse effects. Target and study population. Experimental and comparator or control group. Data management and quality assessment. Missing data. Multi-centre trials. Journals: transparency and reporting guidelines, CONSORT statement, conflicts of interest, publications bias, registration of clinical tests. Decisions by regulatory agencies, SOPs and ICH guidelines.</td>
<td><strong>Specific objectives:</strong></td>
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<tr>
<td>The student will read critically an original clinical trial. She/he will analyze and report it in a transparent and reproducible way.</td>
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### A1: Analysis of parallel trials without baselines

<table>
<thead>
<tr>
<th><strong>Learning time:</strong> 12h 30m</th>
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<tbody>
<tr>
<td>Theory classes: 3h</td>
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<tr>
<td>Practical classes: 1h 30m</td>
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<td>Self study : 8h</td>
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<table>
<thead>
<tr>
<th><strong>Description:</strong></th>
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<tbody>
<tr>
<td>Parallel</td>
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### A2: Analysis of parallel trials with baselines

<table>
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<tr>
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<tr>
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<tr>
<td>Practical classes: 1h 30m</td>
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<tr>
<td>Self study : 8h</td>
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<tbody>
<tr>
<td>Parallel</td>
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### A3: Analysis of cross-over trials

<table>
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<th><strong>Learning time:</strong> 12h 30m</th>
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<tr>
<td>Theory classes: 3h</td>
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<tr>
<td>Practical classes: 1h 30m</td>
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<tr>
<td>Self study : 8h</td>
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<table>
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<tr>
<th><strong>Description:</strong></th>
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<tbody>
<tr>
<td>Statistical analysis, graphic presentation, risk of bias, wording and reporting Baseline measurements. Adjustment, Efficiency. Intra-class correlation.</td>
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</tbody>
</table>
| A5: CT design, protocol and statistical analysis plan | Learning time: 12h 30m  
Theory classes: 3h  
Practical classes: 1h 30m  
Self study: 8h |
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<tr>
<td><strong>Description:</strong></td>
<td>CT design, protocol and statistical analysis plan</td>
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| A5: Regulatory and journal reporting standards | Learning time: 12h 30m  
Theory classes: 3h  
Laboratory classes: 1h 30m  
Self study: 8h |
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<tr>
<td><strong>Description:</strong></td>
<td>SOPs, EMEA, FDA and ICH documentation, Equator and reporting guidelines</td>
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| B1: Ethics, Multiplicity | Learning time: 6h 15m  
Theory classes: 1h 30m  
Practical classes: 0h 45m  
Self study: 4h |
|---|---|
| **Description:** | Experiments, medicine and human rights (independence, autonomy, beneficence). Equipoise and original position.  
Study objectives. Situations requiring more than one test. Hypothesis and family of hypotheses. Alpha risk control: partial and global.  

| B2: Equivalence. Pragmatic trials | Learning time: 6h 15m  
Theory classes: 1h 30m  
Practical classes: 0h 45m  
Self study: 4h |
|---|---|
Pragmatic versus explanatory trials. Consort extension. |
### B3: Sample size rationale.

**Learning time:** 12h 30m  
Theory classes: 3h  
Practical classes: 1h 30m  
Self study: 8h

**Description:**  
Effect size under the alternative hypothesis. Secondary parameters derived from the assumptions (variance, event and recruitment rates, ...). Methods for continuous, dichotomous and time to event variables.

### B4: Randomization.

**Learning time:** 11h 45m  
Theory classes: 3h  
Practical classes: 0h 45m  
Self study: 8h

**Description:**  
Simple, blocks, stratified and adaptive (minimization) randomization.

### B5: Cluster trials

**Learning time:** 6h 15m  
Theory classes: 1h 30m  
Practical classes: 0h 45m  
Self study: 4h

**Description:**  

### B6: Sistematic revisions and meta-analysis

**Learning time:** 12h 30m  
Theory classes: 3h  
Practical classes: 1h 30m  
Self study: 8h

**Description:**  
200627 - AC - Clinical Trials

B7: Adaptative designs

Learning time: 6h 15m
- Theory classes: 1h 30m
- Practical classes: 0h 45m
- Self study: 4h

Description:
Fixed sample designs against adaptive designs. Consumption functions of alpha risk and control. Triangular design. Unbiasedness against shrinkage.

Qualification system

The student mark is the maximum of the final exam and the continuous (C) evaluation.
Mark = Max (F, C)
C is divided in blocks 1 and 2 and each one has 2 parts: Theoretical questions (T, 40%) and Homeworks (H, 60%).
C = 0.2T1 + 0.3H1 + 0.2T2 + 0.3H2
F has 3 parts: Theoretical (T) questions, Exercises (E) and Practices (P), with weights 30%, 40% and 30% respectively:
F = 0.3T + 0.4E + 0.3P

Bibliography

Basic: