CLINICAL TRIALS DESIGN AND EVALUATION OF MOLECULAR THERAPIES

STUDY PLAN 2022-2023

Coordinated by:
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GENERAL INFORMATION

Subject Name	Clinical Trials Design and Evaluation of Molecular Therapies
Code	572714
Type	Optional
Teaching	Second semester
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ECTS credits	3

OBJECTIVES

The purpose of this module is to gain knowledge on the drug development process, and be able to understand the basics of clinical trial design within a product development program.
At the end of this subject, students must be able:

- To list the phases of product development of new chemical entities and understand their objectives.
- To interpret and the type of evidence coming from each phase of product development.
- To understand basic concepts of pharmacokinetics relevant for drug development.
- To discuss the key features of clinical trial design.
- To discuss basic aspects of statistical considerations in clinical trials, including *apriorism*, protection against errors and multiplicity issues.
- To interpret results for comparison of proportions, means and survival analyses.
- To understand the concepts of superiority, equivalence and non-inferiority.
- To explain the terms exploratory, confirmatory, biomarker and validation.
- To explain the main steps to reach a marketing application approval in Europe.
- To know the different interactions with regulatory agencies during a product development process, and their objectives.
- To have notions on post-marketing surveillance and the adaptive licensing initiatives.

COMPETENCES TO BE GAINED DURING THE STUDY

General

G1: Be able to design, plan and properly interpret clinical protocols in the field of Translational Medicine
G2: Be able to dynamically integrate modern knowledge & techniques developed within the field of Translational Medicine
G3: Be able to interact with professionals from other medical specialties in a creative and decisive way
G4: Have a clear appreciation of disciplinary actions and communications necessary to establish the link between basic science and clinical medical research

Specific

S1: To be capable of teaching and divulging knowledge in the social environment for expert and non-expert people

S2: To be capable of integrate knowledge and ways to do in front complex situations and to formulate a judgment with a limited information, but in a reflexive way, taking into account the social and ethical repercussions of them
S3: To be capable of knowing the bioethical and legal principles of research and professional activities in the field of translational research
S4: To be capable of using adequate technologies for the design, analysis and interpretation of epidemiological data
S5: To be capable of identifying problems of public health, to design epidemiological studies and to interpret the results

Pre-requirements

All oral sessions, presentation of lectures and practical sessions will be offered in English, thus students should have a good comprehension and oral English level.

THEMATIC BLOCKS

A) Design of Clinical trials

A.1 Basic applied statistics. Type of Studies. Observational studies and Randomised Clinical Trials (RCT)

- Basic statistics applied to clinical trials. Population and samples. Bias and random errors. Statistical errors.
- Statistical inference: p-values and confidence intervals. Sample Size determinants.
- Study types. Observational vs Experimental designs. Non-Randomised studies.
- Basics of clinical trials. Methods for handling bias. Randomisation. Blinding. Control group. Stratification. Covariates. Study populations. Estimating Clinical Effects: end-points.

A.2 Statistical issues in the Analysis and interpretation of RCT

- Analysis and interpretation of RCT. Handling of Multiplicity. Subgroups.
- Surrogate end-points and biomarkers. Predictive and prognostic factors.
- Interim analyses and stopping rules.
- Non-Inferiority Designs. Selection of the non-inferiority margin. Impact of different end-points types.
- Assessment of events: count, recurrence and censoring. Survival Analysis.

A.3 Practical planification of RCT. Sample size. Alternative designs. Estimands

- Planification of a clinical trial. Regulatory and scientific sources.
- Sample Size predetermination for continuous, binary, count and survival end-points in superiority and non-inferiority trials.
- Basic designs: Factorial, crossover, multi-Arm trials.
- Alternatives to traditional for trial optimisation: adaptive, Bayesian, repeated measurements, withdrawal, enrichment, simultaneous multiple end-points. Umbrella and basket trials.
- Handling of missing data. Impact on estimands.

A.4. Meta-analysis. Data management. Reporting of Clinical Trials.

- Meta-analysis of observational and experimental studies
- Reporting of clinical trials
- Data Collection, data quality, data management and Database

B. Clinical trials – from Phase I to III

B.1 Overview of trial design. Phase I trials

- Overview of trial design, levels of evidence, end-points and magnitude of benefit
- Regular vs accelerated approval
- Phase I –
- Phase I- Examples

B.2 Phase II trials

- Phase II and randomized Phase II –
- Phase II- Examples

B.3 Phase III trials

- Phase III –
- Phase III- Examples

C. Drug development, regulatory issues and safety

C.1 Product development plan. Drug Discovery. Non-Clinical development

- Product development plans and target product profile.
- Drug discovery process, from bench to bed.
- Non-Clinical development and early safety tests.

C.2 Good Clinical Practice. Marketing Authorization Procedures

- Fundamentals of clinical research. International Council for Harmonization, Good Clinical Practice: What do I need to know as a clinical investigator?
- Regular process for Marketing Authorization Procedure. EMA, other drug agencies.

C.3 Real-world data. Safety

- Effectivity assessment and real-world data
- Safety data reporting in clinical trials. Concepts of Adverse Event, Adverse Drug Reaction, SAEs and related safety topics

METHODOLOGY

Total training hours: 3 credits ECTS x 25h/credit = 75h

Face to face lectures: (48h) will include lectures and case studies.
Home training (27h): In order to complete 3 ECTS credits of the subject, students will have to prepare and present one case study based on the concepts explained in face-to-face training.

Classroom activities will consist in sessions which firstly show the conceptual aspects and secondly, problem solving using different case studies. In this way, the students will acquire knowledge and skills to apply translational research by means of the analysis of real situations

EVALUATION

Evaluation criteria:

To pass the subject, students must obtain a minimum of 50/100 points. The score will be established as follows:

• **Attendance:** 50% of the overall grade.
Attendance will be evaluated as: 95%-100% → 50 points / 80% - 95%→ 40 points / 30-80% →20 points / <30% → Subject Failure

• **Oral Presentation and report:** 50% of the overall score. (This will be described in detail during the 1st day of class)

To pass the subject, students will have to fulfill three requisites: Attendance-score ≥ 20/50, oral presentation/report-score ≥20/50, and overall score (attendance + exam) ≥ 50/100.

Reevaluation: In case of failing the ordinary evaluation, students will perform an oral exam. The re-evaluation final score will never get over 50 points.

REFERENCES

Clinical Trials

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- Chow SC, Liu JP. Design and Analysis of Clinical Trials: Concepts and Methodologies. John Wiley & Sons. 2nd Ed. 2004.
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- Libro Luces y Sombras en Investigación Clínica: http://www.fundaciogrifols.org/en/web/fundacio/-/-luces-y-sombras-en-investigacion-clinica- (Chapter 9: Nuevos diseños en investigación clínica), Caridad Pontes, José Ríos, Ferran Torres)

Biomarkers

- Simon R. Genomic Clinical Trials and Predictive Medicine. Cambridge University Press, National Institutes of Health 2013, New York, USA
- Simon R. Clinical trials for predictive medicine: new challenges and paradigms. Clin Trials. 2010 Oct;7(5):516-24.
- Dancey JE, Bedard PL, Onetto N, et al: The genetic basis for cancer treatment decisions. Cell 148:409-420, 2012
- Simon R. The use of genomics in clinical trial design. Clin Cancer Res. 2008 Oct 1;14(19):5984-93.
- Freidlin B, Korn EL. Biomarker enrichment strategies: matching trial design to biomarker credentials. Nat Rev Clin Oncol. 2014 Feb;11(2):81-90.
- Catenacci DV. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Mol Oncol. 2015 May;9(5):967-96.
- Freidlin B, McShane LM, Korn EL. Randomized Clinical Trials With Biomarkers: Design Issues. J Natl Cancer Inst 2010;102:152–160
- Simon R. Clinical trials for predictive medicine. Stat Med. 2012 Nov 10;31(25):3031-40.
- Freidlin B, McShane LM, Polley MY, et al. Randomized phase II trial designs with biomarkers. J Clin Oncol 2012;30:3304-9.
- Simon R. Biomarker based clinical trial design. Chin Clin Oncol 2014;3(3):39

International Conference of Harmonization (ICH)

- CPMP/ICH/363/96. ICH E9 Statistical Principles for Clinical Trials. URL: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500002928, last access: 08-Nov-2010.
  - ICHE9. Addendum: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9_R1_Final_Concept_Paper_October_23_2014.pdf
- Other ICH guidances can be found at: www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

EMA Guidelines

- EMEA Scientific Guidelines for Human Medicinal Products, Clinical Efficacy and Safety Guidelines, Biostatistics. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000602.jsp&mid=WC0b01ac05807d91a4, last access: 04-09-2016.
- EMEA Scientific Guidelines for Human Medicinal Products, Clinical Efficacy and Safety Guidelines, General. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000366.jsp&mid=WC0b01ac0580032ec4, last access: 04-09-2016.

Useful links

- Simon Two-Stage Design:
  http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx
- Sample Size:
  GranMo del IMIM: http://www.imim.cat/ofertadeserveis/software-public/granmo/index.html
  POWER de Un. IOWA: http://homepage.stat.uiowa.edu/~rlenth/Power/
- Power and sample size de Vanderbilt University, by Dupont WD, Plummer: http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize