Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2015

JOANA FERNANDA DURÃES BARBOSA GRANJA

RELATÓRIO DE ESTÁGIO CURRICULAR NA BLUECLINICAL, LDA

CURRICULAR TRAINING REPORT AT BLUECLINICAL, LTD

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Professora Doutora Alexandra Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro e da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical, Lda.

Dedico este relatório aos meus filhos, que são a minha inspiração diária!

o Júri

Presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático Universidade de Aveiro, SACS
Arguente	Professora Doutora Vera Mónica Almeida Afreixo Professora Auxiliar Universidade de Aveiro, Departamento Matemática
Orientador	Professora Doutora Alexandra Isabel Cardador de Queirós Professora Coordenadora Universidade de Aveiro, ESSUA

Agradecimentos

Ao Professor Doutor Luís Almeida, e também ao Professor Doutor Sérgio Simões pela oportunidade de estagiar e trabalhar na Blueclinical, pela atitude visionária, e dedicação com que gerem a empresa.

Ao Professor Doutor Luís de Almeida e ao Professor Doutor Bruno Gago pelo esforço e dedicação na implementação do Mestrado e pela contextualização dos seus estudantes ao mercado de trabalho.

À Professora Doutora Alexandra Queirós e à Doutora Cristina Lopes, por todo o apoio na elaboração deste relatório.

À Doutora Cristina Lopes, por todo o conhecimento que me transmitiu ao longo deste percurso e pela amizade.

A toda a equipa da Blueclinical, que me inspira para ser uma melhor profissional.

A todos os meus colegas de curso, pelo companheirismo e ajuda.

Ao Pedro, por estar sempre presente e me apoiar em todas as decisões.

Aos meus pais e aos meus sogros, que sempre me apoiaram e ajudaram para que pudesse concluir mais este desafio.

A todos, muito obrigada!

Palavras-chave

Blueclinical Back Office, Clinical Research Partnership, Coordenador de Ensaios Clínicos, Ensaios Clínicos, Investigação Clínica.

Resumo

O presente relatório descreve com detalhe o meu período de estágio curricular realizado durante o Mestrado em Biomedicina Farmacêutica.

O estágio teve a duração de 9 meses e ocorreu na Blueclinical Lda., uma empresa constituída por três unidades de negócio distintas: Unidade de Fase I, Unidade de Investigação e Desenvolvimento e uma Unidade de Parceria com Centros de Ensaio - *Clinical Research Partnership* (CRP).

A minha atividade foi desenvolvida apenas numa unidade de negócio – CRP. No entanto tive oportunidade de conhecer duas realidades distintas, exercendo funções num centro de ensaio como coordenadora de ensaios clínicos e funções na Blueclinical *Back Office*, com funções de apoio à unidade CRP, essencialmente na gestão de contratos financeiros e pagamentos.

Neste relatório é revisto o estado de arte da investigação clínica e são descritas as principais atividades realizadas durante o estágio. São igualmente relatadas, as principais dificuldades sentidas, as estratégias utilizadas para as ultrapassar e objetivos que considero alcançados.

A realização deste estágio foi uma excelente oportunidade que me permitiu consolidar os conteúdos teóricos adquiridos durante o primeiro ano do mestrado, obtendo a experiência necessária para ingressar no mundo de trabalho da Investigação Clínica.

Keywords

Blueclinical Back Office, Clinical Research Coordinator, Clinical Research Partnership, Clinical Trials, Clinical Research.

Abstract

The present report describes in detail my internship period, during the Master in Pharmaceutical Medicine.

The internship lasted 9 months and was performed in Blueclinical Ltd., a company that has three business units: Phase I Unit, Research and Development Unit and Clinical Research Partnership Unit (CRP).

My activities were performed in only one business unit - CRP, however I had the opportunity to experience two different realities, exercising functions as Clinical Research Coordinator at site and support functions at Blueclinical Back office, mainly contract management and payment tracking.

This report reviews state of art of clinical research and describes main activities performed during internship. Along with the description of the activities performed, it is done a presentation of the difficulties encountered, strategies used to overcome them and objectives I considered achieved.

This internship was a great opportunity that allowed me to consolidate theoretical knowledge acquired during the first year of the master, giving me the necessary experience to cross into Clinical Research job market.

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LIST OF ABBREVIATIONS

AB	Administration Board
CEC	Centro de Ensaios Clínicos
CEIC	Comissão de Ética para a Investigação Clínica
CLIC	Clinical Investigator Certificate
CMDT	Complementary Means Diagnostic Therapeutic
CNPD	Comissão Nacional de Proteção de Dados
COD	Clinical Operations Director
CPI	Critical Path Initiative
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRP	Clinical Research Partnership
CRO	Clinical Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
FA	Financial Agreement
FDA	Food and Drug Administration
GACEC	Gabinete de Apoio ao Centro Ensaios Clínicos
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
IMP	Investigational Medicinal Product
IMI	Innovative Medicines Initiative
INFARMED	Instituto Nacional Farmácia e Medicamento
IVRS	Interactive Voice Response System
IXRS	Interactive Voice/Web Response System
IWRS	Interactive Web Response System
LCRM	Local Clinical Research Manager
MP	Managing Partner
NCA	National Competent Authority
NHS	National Health System
NME	New Molecular Entity
PC	Person of Contact
PI	Principal Investigator
PIP	Paediatric Investigation Plan
POC	Proof of Concept
PUMA	Paediatric Use Marketing Authorization
QMS	Quality Management System
R&D	Research & Development
SIV	Site Initiation Visit
SOP	Standard Operation Procedure
SQIC	Sistema de Qualidade de Investigação Clínica
TMF	Trial Master File
ULSM	Unidade Local de Saúde de Matosinhos

1 INTRODUCTION

The Master´s Degree in Pharmaceutical Medicine provides competences in the research, development, evaluation, approval and marketing of drugs and other health products. In the second year of the master, we are given the possibility of a practical component with an internship in a pharmaceutical company. I choose this practical component, believing it would be a great opportunity to consolidate the theoretical knowledge acquired in the first year and to promote integration into employment.

This report describes my internship at *Blueclinical - Investigação e Desenvolvimento em Saúde, Lda.*, hereinafter designated "Blueclinical". It took place from 15th September 2014 until 17thApril 2015, supervised by Doctor Cristina Lopes, Clinical Operations Director from Blueclinical and Doctor Alexandra Queirós from University of Aveiro.

Blueclinical is composed by three business units and I developed my internship at Blueclinical Clinical Research Partnership (CRP). During two months I performed functions as Clinical Research Coordinator (CRC) at Local Health Unit Matosinhos - *Unidade Local de Saúde de Matosinhos* (ULSM), and then, I assumed functions at Blueclinical Back Office, performing tasks as contract manager, payment tracking, among others.

1.1 CURRICULAR INTERNSHIP OBJECTIVES

During my internship the main objectives established were divided in primary and secondary objectives.

The primary objectives were:

- Understand regulatory framework of clinical studies;
- Perform study coordinator activities, understanding all activities performed in clinical research during the different phases of a clinical trial at site (starting in feasibility and ending in closeout visit) and the required specific needs associated with each stage;
- Help in the start-up process of a study, reviewing financial contracts;
- Perform strategies for payment tracking.

The secondary objectives were:

- Achieve a multidisciplinary experience contacting with the different business areas of Blueclinical;
- Develop interaction capabilities with multidisciplinary teams, as well as ability to plan and manage activities and the ability of multitasking;
- Integrate the company's policy of quality;
- Contribute with new ideas for development of the company showing a critical attitude.

1.2 HOST INSTITUTION AND PARTNER HOSPITALS

1.2.1 **BLUECLINICAL LTD**.

Blueclinical is a Portuguese company created in May 2012, headquartered in city of Oporto. It is structured in three core business units, which provide services covering different phases of drug discovery process, from bench to bedside. Blueclinical´s logo is composed by three different tones of blue that represent the three business areas, in which Blueclinical operates. A brief description of these areas is provided below, giving more relevance to the unit where I developed my internship, Blueclinical CRP (1):

- **Blueclinical R&D -** There are several public and private companies investing in basic research and therefore, with potential to be translated into new therapeutic medicines and health products, which require experienced partners. Blueclinical Research and Development (R&D) mission is to boost translational research in Portugal, supporting these companies, namely start-ups in the development of their projects towards commercialization.

  Blueclinical R&D provides expert advice on the creation of pharmaceutical, pre-clinical, clinical and regulatory development plans of new drugs, preparation of scientific advice, and preparation of investigator brochure and investigational medicine dossier, business development plan, portfolio selection and funding application (2).
- **Blueclinical Phase I -** It is the next logic step in the value chain. New R&D models emphasize the role of these studies in translational medicine. Blueclinical Phase I

mission is to conduct phase I clinical trials, in healthy volunteers or selected patient populations (early proof of concept). Trials are conducted in a dedicated unit with 29 beds, located in the Hospital of Prelada, Oporto. This unit creates opportunities for the development of earlier phases trials, in Portugal (3).

- **Blueclinical CRP -** Blueclinical CRP mission is to support clinical research activities at sites, promoting their growth, efficiency and gaining excellence reputation in clinical research. Blueclinical CRP established partnerships with several hospitals.

1.2.2 BLUECLINICAL CRP

The Blueclinical CRP will be more detailed in this section because it was the unit where I developed my internship.

Actually Blueclinical CRP has partnerships with thirteen institutions as described in Figure1 (4). These partnerships are achieved through a collaboration agreement between Blueclinical and each institution that leads to the creation of dedicated structures to support clinical research activities. The name given to this structure varies according to institution.

Figure 1 - Blueclinical CRP Network. Logotypes of Institutions and Research offices created due to partnership with Blueclinical (4).

The main functions of support office performed by Blueclinical in these institutions are described below:

- Organize, verify and submit the application for approval of the study to the Administration Board (AB) and to the Competent Ethics Committee (EC) (if applicable);
- Assist clinical team in the identification of potential participants;
- Organize visits of the participants in the study, including the logistical aspects associated with transport, if any;
- Organize internal logistics associated with the study, for example the use of complementary exams, medical tests and pharmaceutical services;
- Organize the logistics related to the sending of biological samples to the outside, if necessary;
- Proceed to fill in administrative forms and Case Report Form (CRF) that do not have to necessarily be filled by members of the clinical team;
- Organize and update the Trial Master File (TMF) of the study;
- Function as person of contact (PC) for monitors and auditors of the sponsor;
- Keep up to date register of activities to be invoiced to the sponsor and inform site about the values and invoice dates, in accordance with the financial agreements;
- Make the preparation of audits and inspections, and organize the implementation of any corrective and preventive measures.

Blueclinical CRP also supports investigators in studies of their own initiative, providing templates of essential documents, helping with regulatory submissions, statistics and publications. This support is not charged for affiliated investigators.

The two main pillars for Blueclinical CRP are quality and training. Blueclinical CRP wants to implement a Quality Management System - *Sistema de Qualidade em Investigação Clínica* (SQIC) at sites. Clinical research related activities are performed under a quality management system that standardizes critical clinical research activities, thus assuring higher efficiency and compliance with good clinical practices and the legal and ethical requirements. A draft quality manual was presented to all institutions, and is being reviewed by AB. Relating to training, Blueclinical CRP stimulates and supports certification of investigators in clinical research offering the Clinical Investigator Certificate (CLIC) explained in further detail at later stages in this report (5).

1.2.3 UNIDADE LOCAL DE SAÚDE DE MATOSINHOS, E.P.E.

ULSM was established in 1999 and is composed by the following units of care:

- Primary Care Units;
- Pedro Hispano Hospital;
- Convalescence Unit (6).

Figure 2 - Hospital Pedro Hispano (ULSM, EPE) (6).

My internship took place in Hospital Pedro Hispano shown in Figure 2. For all institutions described in Figure 1, partnership is achieved through a collaboration protocol between the institution and Blueclinical. For ULSM, this protocol was established in 18 June 2013. This collaboration protocol leads to the creation of a dedicated structure to support clinical research activities. The name given to this structure varies according to institution´s organogram. In ULSM, the existent structure dedicated to clinical research is Clinical Trial Center - *Centro de Ensaios Clínicos* (CEC) and with the partnership, Support Office of Clinical Trial Center - *Gabinete de Apoio ao Centro de Ensaios Clínicos* (GACEC) was created.

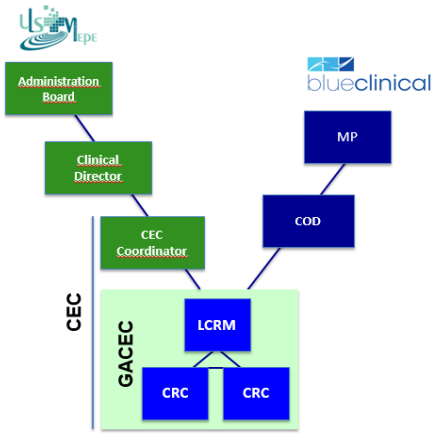

Figure 3 - Structure of Research Office at ULSM, E.P.E.

CEC - Centro de Ensaios Clínicos; **COD** - Clinical Operations Director; **CRC** - Clinical Research Coordinator; **GACEC** - Gabinete de Apoio ao Centro de Ensaios Clínicos **LCRM** - Local Clinical Research Manager; **MP** - Managing Partner (5).

In ULSM, CEC is constituted by:

- **Coordinator** - Physician named by the AB that coordinates CEC. Coordinator will report to clinical director or his representative and to AB.
- **GACEC -** supporting office constituted by workers from Blueclinical CRP: Local Clinical Research Manager (LCRM), and one or more CRC. All human resources from GACEC are qualified to operationally support activities from coordinator and clinical investigators. GACEC reports their activities to Clinical Operations Director (COD) that will report to Managing Partners (MP) of company. All CRC from Blueclinical sign a confidentially agreement with institution, as they will have to deal with sensible data like patients files.
- **Clinical Investigators** that desire to become affiliate with CEC. Clinical investigators are health professionals who want to associate with CEC. They should undergo a training plan in clinical research that will be provided free of charge by Blueclinical - CLIC (7).

1.3 REPORT'S STRUCTURE

This report is structured in the following chapters:

- Introduction: Provides an overview of company and site where I performed my internship. It also establishes my primary and secondary objectives for my training period.
- State-of-the-Art: This chapter describes regulatory environment of clinical research, the change of paradigm in clinical development and clinical research in Portugal.
- Experience: Details activities performed during my internship at site and at Blueclinical Back Office.
- Discussion: Identifies difficulties and challenges felt during internship, as well as learning outcomes and competences developed.
- Conclusion: Integrates a summary of what internship offered me.

2 CLINICAL RESEARCH STATE OF ART

2.1 ETHICAL AND REGULATORY CONTEXT

Laws and ethical codes apply to the different stages of drug development, aiming to maximize public protection. Conduct of clinical research in human beings brings into discussion ethical issues of extreme importance, and in order to achieve the ultimate goal of protecting public health, clinical research is highly regulated. In European Union (EU), regulatory framework can be a regulation, directive, guidelines or reflection papers. Regulations have an immediate application for all member states, while directives have to be transposed into national law. Guidelines or reflection papers are not legally binding, but they try to provide the best or most appropriate approach to fulfill legal obligations, representing EU harmonized position. The use of different approaches requires justification. European Medicine Agency (EMA) is responsible for the scientific evaluation of medicines. It started its activity in 1995, is located in London and is the one responsible to protect and promote public health and animal health through evaluation and supervision (8). EMA regulates activity of 27 countries and 3 additional countries from the Economic European Area (Iceland, Norway and Lichtenstein).

Figure 4, represents chronologically, the most relevant regulatory environment in clinical research.

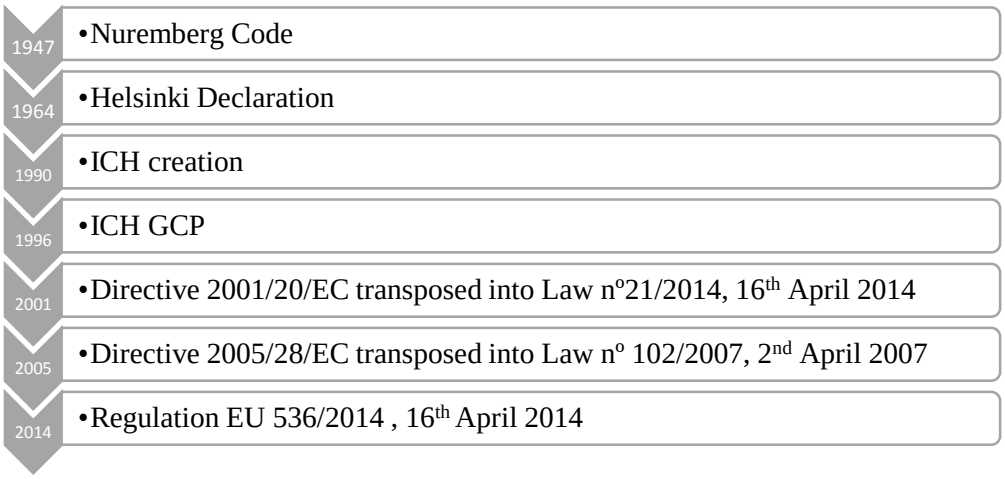

Figure 4 - Milestones in Clinical Research Regulatory Environment.
ICH - International Conference on Harmonization; **GCP** - Good Clinical Practice. Adapted (10, 11, 18).

At the end of the Second World War, after the atrocities committed with human experimentation, the Nuremberg Code was written in 1947, and dictates 10 basic principles by which clinical research in humans should be governed. The principles of the Nuremberg Code were extended and improved through the Declaration of Helsinki. This declaration, established in 1964 is considered the first international standard which describes that welfare of human beings is given priority over the interests of science and society, and had its origin in Nuremberg Code (9). It covers all important ethical considerations involved in clinical research, involving human subjects. According to this declaration the most important items are putting the well-being and safety of the subjects in front of science, the need of informed consent, review of ethical committee, involvement of qualified persons in the trial and application of scientific standards in the design of trial (9,10).

After the thalidomide tragedy in Europe, safety and efficacy uncertainties about new drugs, increased the costs of research. In order to reduce costs and avoid duplication of the work, in 1990 regulatory authorities from EU, Japan and USA and experts of pharmaceutical companies joint to reach consensus about the requirements for the authorization of new products which resulted in the creation of International Conference on Harmonization (ICH), which mission is to achieve harmonization, while ensuring safe, effective and high quality medicines (10). This harmonization led to an economic use of animal, human and material resources, facilitating mutual acceptance of data by regulatory authorities in these jurisdictions. ICH has two essential goals: protect the rights, integrity and confidentiality of participants, and quality and integrity of the data collected (11).

In 1996, was created the ICH E6 (R1) - Guideline for Good Clinical Practice (ICH - GCP), that is an internationally accepted standard dictated by the ICH based on the principles of universal Declaration of Helsinki, that sets out the principles for planning, conducting, and monitoring of clinical trials (12). Since the implementation of ICH - GCP, clinical trials evolved, and innovative approaches must be considered, for the appropriate use of technology. For this reason, in June 2014 was implemented ICH E6 (R2) - Addendum to Good Clinical Practice, that implements innovative approaches as quality risk management and quality by design process (13).

Conduct of clinical trials of medicines is regulated in EU by Directive 2001/20/EC, known as Clinical Trial Directive. According to Directive 2001/20/CE a clinical trial is considered "Any investigation in human subjects intended to discover or verify clinical,

pharmacological and / or pharmacodynamics effects of one or more investigational medicinal products and / or identify any adverse reaction to one or more investigational medicinal product and / or analyze the absorption, distribution, metabolism and elimination of one or more investigational medicinal in order to determine their safety and / or efficacy." (14, p.5). Non interventional studies are excluded from the scope of this directive. Investigational Medicinal Product (IMP) is considered an "active ingredient in a pharmaceutical form or placebo being tested or used as a reference in a clinical trial, including products already with marketing authorization in the market but used or formulated differently from the authorized form, or used for an unauthorized indication, or intended to obtain further information about the authorized form" (14, p.6). Medicines with marketing authorization and placebo are also included in this definition. This directive aims to ensure human rights and harmonize procedures and requisites for the authorization of clinical trials by regulatory authorities and EC. Before this directive, European countries varied a lot in terms of the procedures and requirements for the conduct of clinical trials. This directive establishes a legal bond for the implementation of ICH - GCP, implementation of Good Manufacturing Practices (GMP) and establishment of a system for collecting and sharing information (information transparency). Clinical trial directive established two databases: EudraCT, an electronic database for interventional studies and Eudravigilance clinical trials module, a database for European report of suspected unexpected serious adverse reaction. It also ensures the protection of personal data (14). Directive 2001/20/CE was firstly transposed into Law 46/2004, 24th August, and then transposed into Law 21/2014, 16th April, that has a broader scope of application, regulating all clinical research covering beyond clinical studies with medicinal products for human use, studies with medical devices, cosmetics and hygiene products (15).

Directive 2005/28/CE, also referred as GCP directive lays down the principles and guidelines regarding IMPs for human use (16) and provides more detail on requirements of clinical trial directive. It was transposed into national Law 102/2007, 2nd April 2007.

Directives and guidelines governing medicinal products in Europe can be found in volume 10 (Eudralex) - The rules governing medicinal products in European Union, published on European commission website.

Several criticisms were made to clinical trial directive, saying it led to a decrease in clinical trial authorization, increasing costs and human resources needed for the clinical trial

authorization process (17). Harmonization impact expected from this Directive 2001/20/CE was hindered as directive requires transposition into national law, and similar, but different interpretations where obtained from the different member states. On the other hand, impact of this legislation on the structure and activity of competent authorities led to an increased need of resources and a consequent application of a tax to the sponsor.

On 16th April 2014 was published the new European regulation of clinical trials EU 536/2014 revoking Directive 2001/20/EC. The objective of this regulation is to create a favorable environment for clinical research in Europe, contradicting the trend of delocalization of this activity to emerging countries. This new regulation proposes introduction of a new clinical trial authorization procedure. Main alterations are described below:

- Harmonized authorization dossier, the submitted file is divided into part I intended to be assessed jointly by all Member States and part II to be assessed at national level, only;
- Authorization requests of clinical trials connected to an EU database, free of charge to the sponsor;
- Possibility of tactic authorization;
- More flexible and rapid assessment;
- Clearer timelines;
- Possibility of sponsor being located in third countries provided that there is a contact person in the EU;
- Differentiation of clinical trials based on risk: clinical trials of minimal intervention and not minimal intervention;
- Responsibility of member states to define the organizational structure and internal competences for assessing clinical trial authorization application;
- Adaptation of insurance rules;
- Permission for co-promotion (18).

The new regulation came into force on 6th June 2014, but nevertheless will only apply 6 months after publication of the notice of the European Commission to the portal operation of the United States and EU entry database. This regulation is expected to be in practice only in 2016 (17).

Clinical research is a demanding and complex activity that requires the involvement of various stakeholders (Figure 5):

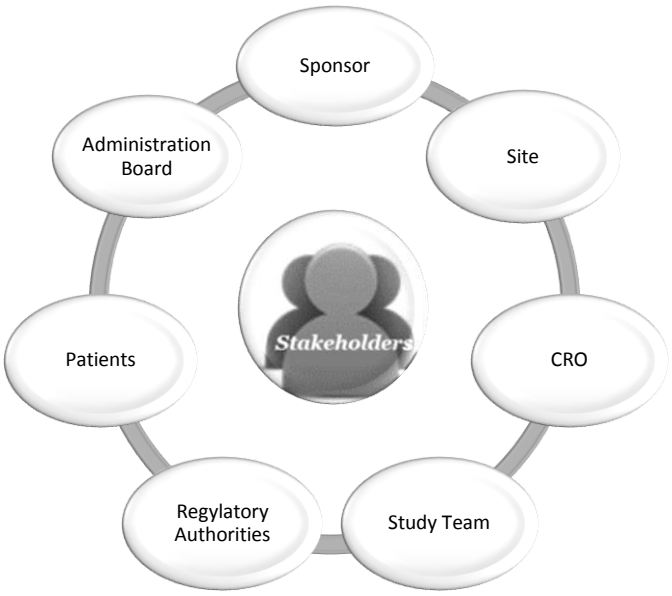

Figure 5 - Main Stakeholders in Clinical Trials. Adapted (19).
CRO - Contract Research Organization.

- **Sponsor -** Usually is a pharmaceutical company or can be investigator, in case of studies from their own initiative. Sponsor is the one that takes responsibility for initiation, management and financing of the study.
- **CRO -** Contract Research Organization is an organization contracted by the sponsor to perform one or more of his functions. The last responsibility is always from the sponsor.
- **Study team -** constituted by Principal Investigator (PI) and all team needed to conduct the study. It may include, sub investigators, nurses, study coordinators, laboratory technicians, pharmacists and others.
- **Clinical trial site -** is the physical place where trial activities are conducted.
- **Administration Board -** studies need approval from AB of the site in order to be conducted.
- **Subjects -** can be healthy volunteers or patients.
- **Regulatory Authorities -** Sponsor has to submit an application for clinical trial authorization to National Competent Authority (NCA), and EC (19). If the trial is conducted in more than one Member State, application must be repeated for each Member State. First, Sponsor should acquire the unique EudraCT number from EudraCT database. Application details for NCA are described at volume 10 of

Eudralex and should include covering letter, EudraCT number, clinical trial application form, protocol, investigator brochure (or summary of product characteristics in case of a product with a marketing authorization) and investigational product dossier. NCA has 60 days to consider a valid request. NCA evaluates medicines, pharmaceutical quality, pre-clinical and toxicological data, pre-existing clinical data, safety monitoring.

Application for EC is also established in chapter I of volume 10 of Eudralex. EC evaluates on pertinence of trial and trial design, balance risk / benefit, suitability and experience of research team, quality of facilities, adequacy of written consent, recruitment form, indemnity and compensation in case of injury and inclusion of vulnerable population. EC has also 60 days to evaluate a valid request.

In Portugal, NCA is represented by *Instituto Nacional da Farmácia e do Medicamento* (INFARMED) and EC is represented by *Comissão de Ética para a Investigação Clínica* (CEIC) (19). To conduct a trial in Portugal, submission is performed to INFARMED, CEIC, *Comissão Nacional de Proteção de Dados* (CNPD) and AB from site (20).

2.2 NEW CLINICAL RESEARCH PARADIGM

Pharmaceutical industry is facing a challenging period. Expenditures in R & D are rising resulting from a stricter regulatory environment, but this spending is not being reflected in an increased number of New Molecular Entities (NME) launched into the market. The loss of productivity is due to the increasing competition, patent cliff, the arising of generics market and stricter regulatory environment. Development of a NME takes in average 13 years and costs of drug development are increasing. The need for a more efficient drug development plan, is actually recognized by all stakeholders (21).

Before a drug can be launched into the market, extensive pre-clinical and toxicological studies are performed. Clinical trials are the most expensive part of drug development. They may be classified according to their objectives or according to time of study occurrence in clinical development. Usually clinical drug development is designated in four temporal phases (I to IV). This is the traditional classification, but is not always suitable as one type of study may occur in several phases. A fixed order in clinical development plan is not always needed. Nowadays a classification based on type of study is more indicated.

Analyzing Figure 6 we can see that types of study are usually associated with a certain phase of development. Nevertheless, other type of studies may occur at that development stage, although it is less common (22).

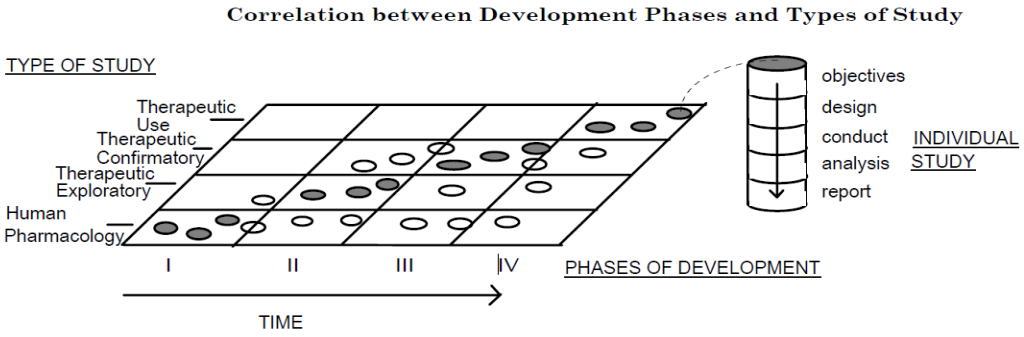

Figure 6 - Correlation between Development Phases and Types of Study (22).

The four development phases used in clinical drug development are:

- **Human Pharmacology studies (phase I) -** Typically associated with phase I studies, may also be conducted in other stages. These studies usually don't have therapeutic objectives and are conducted in healthy volunteers. Main objectives are to assess tolerance, describe PK/ PD, explore drug metabolism and drug interactions, and estimate activity.
- **Therapeutic Exploratory (phase II) -** Usually phase II. Primary objective of these studies is to explore therapeutic efficacy in patients. This studies will help to determine the dose and regimen for phase III trials (therapeutic confirmatory). They provide basis for confirmatory study design, endpoints and methodologies.
- **Therapeutic Confirmatory (phase III)** - Intend to demonstrate or confirm therapeutic benefit. They will confirm evidence accumulated on phase II, in order to assure drug is safe and effective for intended indication and in receiver population. They provide the basis for marketing approval, establishing safety profile, assessing risk/ benefit in order to support licensing, establishing dose response relationship, assessing risk/ benefit in wider populations, in different stages of disease and with different concomitant medication.

- **Therapeutic Use (phase IV) -** Starts after drug approval. These studies are important for optimizing drugs use. They intend to re access risk/ benefit relationship in general populations, or environments, refine dose recommendation and identify less common adverse reactions. These studies may also be performed for the development of an application unrelated with original approval use (new dosage regimens, new route of administration, new indication) (22).

Classis paradigm for clinical research, described from phase I to IV, is very lengthy, costly and very low predictive of safety and efficacy. In this traditional model, new entities fail in later and expensive phases of development (21). In new model called "quick win, fast fail", uncertainty is decreased before expensive later stages of development. This directs resources for new molecules that have higher probability to succeed. Savings gained with this new model can be re invested to further enhance R&D productivity (Figure 7) (21).

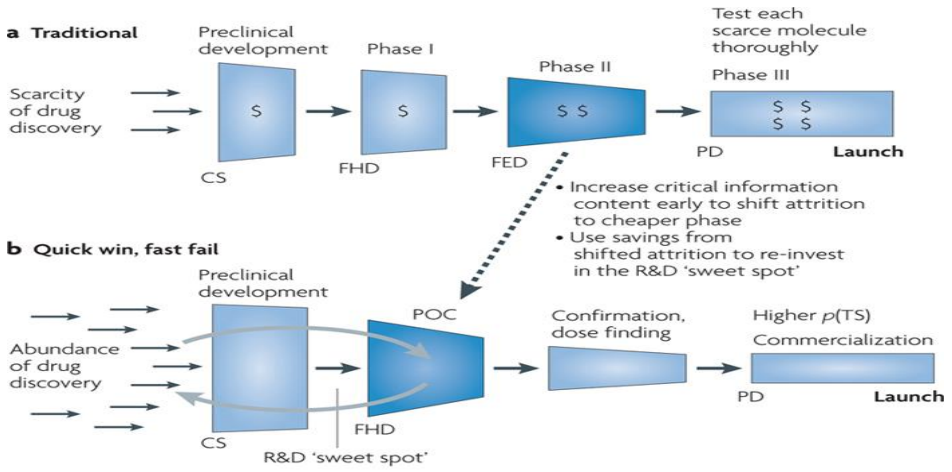

Figure 7 - Traditional versus New Research Paradigm (21).

This new model arises from the need of a more flexible model that takes advantage of all technologies, disease modeling, adaptive clinical trials, biomarkers and baysean-style statistical approaches. Advances in basic sciences especially the biotechnology advances in molecular targeting, immunology and omics sciences created a great opportunity for development, providing a good knowledge of diseases and its mechanisms. This new model is based in life testing and life licensing. There wouldn't be only a submission for marketing authorization, but many submissions occurring during development, allowing limited launch. At the beginning, NME would be only available for a subgroup of population. As

more information on safety and efficacy is available, then new submissions to authorities are performed and extended to large populations. This new paradigm is also known as quick win fast fail, because it wants to bring uncertainty to the earliest phases of development directing resources for molecules that have a higher probability to launch. In this model, Proof of Concept (POC) is created with the objective of testing as soon as possible new medicines in humans. Here, is where a lot of molecules fail (21).

Studies can also be classified as interventional (or experimental) or non-interventional (or observational). Non-interventional studies can be categorized as cross-sectional, cohort, or case-control, according to the objective of the research study. Main differences are described in Table 1 (adapted 23).

	Experimental	**Observational**		
Study Design	**Randomized Control Trial**	**Cross-sectional**	**Cohort**	**Case-Control**
Study Population	Highly selected population	Diverse Population in a range of settings	Diverse Population in a range of settings	Diverse Population in a range of settings
Directionality	Exposure is assigned before outcome is ascertained	Exposure and Outcome ascertained simultaneously	Exposure ascertained before outcome is ascertained	Outcome is ascertained before exposure is ascertained
Primary Use	Demonstrate efficacy of an intervention	Screening Hypotheses; prevalence studies	Assessing association between multiple exposures and outcomes over time.	Assessing associations between exposures and rare outcomes
Analysis	Straight forward	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding
Internal Validity	High	Low	Low	Low
External Validity	Low/Moderate	High	High	High

Table 1- Comparison between Experimental and Observational studies. Adapted (23).

As times progresses it becomes more difficult to discover new innovative drugs. Pharmaceutical companies need to distance themselves from blockbuster approach because casual discovery of "one size fits all" is difficult, lengthy and costly. If companies are not willing to take risks, there will not be innovation (21). Many resources are applied and allocated to "low hanging fruits" and efforts made in same disease areas, where return on

investment can be quicker. Industry of similar and generics is rising because this market has a cheaper and quicker development that offers much less risk.

In order to mitigate these hurdles, authorities created benefits for medicines that fulfill unmet medical needs. Regulation EC 141/2000 provides incentives to stimulate innovative medicines such as fee reduction/ exemption, market exclusivity, scientific advice and protocol assistance, community marketing authorization and national incentives (24).

Food and Drug Administration (FDA) created a draft guidance for adaptive design for clinical trials. Clinical trials are planned with adaptive features that can make studies more efficient (shorter duration, fewer patients), more likely to show effect of a drug if it exists, or other important information. Key value of adapting is not in reducing sample size, but increasing the information value, thus making adaptive designs more ethical/ efficient (25).

In addition, other initiatives are being made to address decreased R&D productivity. Two examples are the FDA's Critical Path Initiative (CPI) established in 2004 and European Innovative Medicines Initiative (IMI) created in 2007. IMI is a public partnership that involves Pharmaceutical Industry and is represented by European Federation of Pharmaceutical Industries and Associations and European Commission. IMI activities aim to develop medicines safer and faster. IMI research agenda focus on four pillars: prediction of safety evaluation, prediction of efficacy evaluation, knowledge management, education and training. IMI intends to accelerate discovery and development of new medicines in the area of cancer, inflammatory and infectious diseases, between others (26). CPI identifies opportunities that could be implemented in order to increase productivity of drug development. It is essentially based in the development of better evaluation tools, development of biomarkers and better knowledge of the disease, streamlining clinical trials, making use of advances in bioinformatics, moving manufacture to 21st century, and increase the development of medicines addressed to medical unmet needs and risk populations, like children (27).

Paediatric Investigation Plan (PIP) and Paediatric Use Marketing Authorization (PUMA) are initiatives from EMA that play an important role in the development of medicines for paediatric (28).

EMA created a Roadmap 2015 in order to accelerate evaluation and development of medicines for the benefit of public health. Here, objectives and priorities are established since 2011 to 2015. Strategic areas are addressing public health needs (stimulation of

medicines for unmet medical needs, medicines for rare diseases and all types of veterinary medicines), facilitating access to medicines (implementing activities to reduce productivity gap that nowadays exists in drug development) and optimizing safe and rational use of medicines (29).

2.3 CLINICAL RESEARCH IN PORTUGAL

Clinical trials are the most expensive part of drug development. Stakeholders point cost of clinical trials as a barrier to innovation (30). In order to save time and money, industry is increasingly seeking for countries that can offer the best conditions to perform clinical trials. In recent years, Portugal has revealed a progressive loss of competitiveness with a reduction in the number of clinical trials conducted, which is among the lowest rates in Europe. Large pharmaceutical companies are moving clinical trials out of Portugal, mainly Eastern Europe, Asia and Latin America which have seen an exponential growth in clinical studies. In 2014, 5549 clinical trials were conducted in Europe, but only 127 were performed in Portugal (31). Clinical research is an activity that presents a very high return on investment. It is estimated that for 1 € invested the return will be 1.98 € which is almost the double (32).
Clinical trials can bring a lot of benefits for our country (economic, political and social), but the most important ones are undoubtedly early access to innovative treatments, reduction of public expenditure, job creation, and increase in tax revenue positive - impact on the trade balance of the country (19).

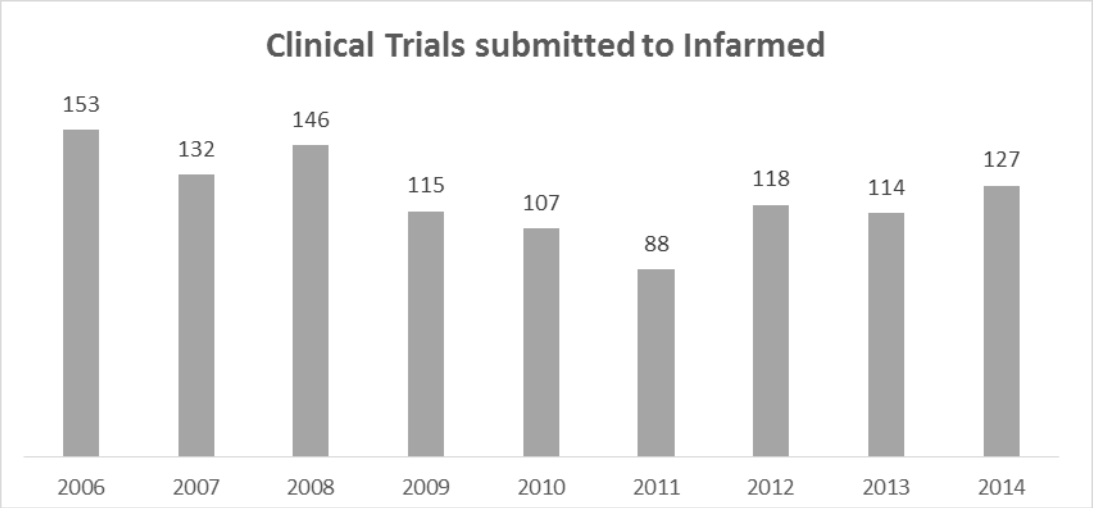

Figure 8-Number of clinical trials submitted to INFARMED (2006-2014). Adapted (33).

Figure 8 shows the number of clinical trials submitted to INFARMED between 2006 and 2014. Between 2006 and 2013 the number of clinical trials submitted in Portugal decreased. The year of 2011 reached the lowest number with 88 trials. In 2014, it seems to be a slight increase in number of clinical trials submitted (33). Efforts are being made in Portugal to change this scenario.

Year	Phase I	Phase II	Phase III	Phase IV	Total
2006	2	20	104	27	153
2007	7	30	74	21	132
2008	3	31	100	12	146
2009	6	27	73	9	115
2010	2	17	79	9	107
2011	6	19	58	5	88
2012	3	25	82	8	118
2013	10	20	75	9	114
2014	10	24	81	12	127

Table 2 - Clinical Trials submitted to INFARMED per phase of Development. Adapted (33).

As shown in Table 2, phase III and IV represent about 80 % of trials in Portugal. Phase I has almost no expression, (compared with other countries) and only 8 trials were made between 2008 and 2012. Between 2013 and 2014 this number raised to 10 per year, which is due to the creation of Blueclinical Phase I. Also, therapeutic areas with more clinical trials are antineoplastic and immunomodulation agents, central nervous system, cardiovascular system and anti-infectious. Portugal as potential to grow in early stages and in different therapeutic areas (33).

Compared with other countries, Portugal has a small number of sites participating in clinical trials as well as number of patients recruited. It is needed the approval of four entities (INFARMED, CEIC, CNPD and AB) which leads to an average approval time of a clinical trial in Portugal of about 6 months. On the other hand, we have restrictions on advertising of clinical trials and investigators do not have career incentives in clinical research. Hopefully, this scenario is changing as there is high political endorsement resulting in more competitive timelines from INFARMED and CEIC and the creation of structures dedicated

to clinical research within public health institutions. A new law for clinical research was approved in 2014, but there is still room for improvement.

A study performed by *Associação Portuguesa da Indústria Farmacêutica* in 2013 suggests initiatives that could narrow the gap between Portugal and Europe. Portugal can follow the examples of other countries to understand what could potentiate increase of clinical trials. Some of the measures proposed are revision of legislation for the approval process and revision of legislation for advertising clinical trials (actually advertising is very restrictive falling into medicinal products advertising), as dissemination and publicity could increase Portugal´s ability to recruit. Other proposed measures are revision of the clinical research component in the career development of researchers, creation of structures dedicated to clinical research and review of legislation to promote research of academic nature (19).

A favorable legislative environment coupled with interested researchers and institutions is extremely important but above all Portugal needs sponsors willing to develop clinical trials here. Unfortunately most of the times, Portugal is not considered an option and lack of information still exists about the potential that Portugal may have in clinical research (19).

In 2013 the company Blueclinical CRP established partnerships with various public hospitals in a strong attempt to promote clinical research.

For the success of clinical research in Portugal we have to look to the interests of all involved stakeholders: patient, investigators, institutions, society and sponsors.

3 EXPERIENCE

My training experience was mainly divided between two major functions:

- CRC (two months);
- Blueclinical Back Office, mainly as contract manager (seven months).

This chapter intends to describe activities performed during the time dedicated for each function. One more section is added to this chapter in order to describe other tasks performed during my internship.

3.1 EXPERIENCE AS CLINICAL RESEARCH COORDINATOR

During my internship I performed functions as CRC at ULSM. This experience was short, but provided me an overview of the different and interrelated activities performed at site during a clinical trial.

3.1.1 FEASIBILITY

Site is the physical place where clinical studies can be conducted. Sponsors are increasingly focusing in the correct choice of the site. Feasibility questionnaire intends to assess site´s conditions. Feasibility is an important step as the choice of the site can help to manage costs and may be critical for the success of the study. Site should produce reliable, reproducible data and produce it in a timely and safe manner. Sponsor is looking for short approval process, experienced and motivated teams, necessary facilities and equipment, time to conduct the study and patient enrollment capability. For this reason, feasibilities questionnaires are usually similar and focused in questions about submission process and timelines, facilities and equipment, number of patients with target disease seen by site in one month, recruitment experiences from past, recruitment strategies, competitive trials and experience of study team (34). Feasibilities could be on paper or online but usually both of them are extensive and not very appealing to fill. Sponsor´s first contact is usually by phone or by feasibility survey e-mail. Sponsor provides few information about the study like the name of active substance, title of protocol and disease and tries to assess the potential interest

of institution/ PI in that trial. Then, sends a confidential disclosure agreement to be fulfilled by PI that states that PI will not disclose any confidential information contained in protocol synopsis or questionnaire sent.

As a CRC, feasibilities were a difficult step as I felt some resistance in the filling of these extensive and time consuming questionnaires. Physicians are always much occupied and sometimes could not understand the importance of answering this questionnaire that most of the times had narrow deadlines. This issue was mainly overcome, trying to help physicians answering feasibilities. Usually I printed questionnaire and tried to evaluate which questions I could answer, to optimize this process (such as facilities questions or about submission process) and minimize time spent by physicians answering these questionnaires.

Blueclinical has a person responsible for feasibility management. Feasibities could come directly to institution or from Blueclinical Back Office. My colleague always tried to expand questionnaire from our site to our CRP network, to maximize the possibility of site selection within our CRP network.

Feasibilities are an extremely important step as they will dictate the possibility of site selection.

3.1.2 SITE QUALIFICATION VISITS

Assessment of site conditions may include face-to-face visits. These are called site qualification visits. Sometimes this step is suppressed in order to minimize costs. Sponsor staff visits the site and most of them have checklists of requirements that site should have for selection. During my internship I had opportunity to attend one selection visit from one sponsor. In this visit, me and my colleagues scheduled an appointment with key site staff and departments in order that sponsor could check available resources, maintenance and calibration of equipment, workload of the site and staff competence. Study team Curriculum Vitae (CV) and GCP training are usually requested.

3.1.3 INVESTIGATOR MEETINGS

After site selection, investigators meetings are performed. Competence of PI and site team is site´s responsibility but it is sponsor´s responsibility to provide training in protocol related procedures. All staff working in the trial should have GCP course, but meetings are an opportunity to meet other investigators and to obtain expert advice on trial procedures and study design. Investigator meetings are usually attended by PI and key elements of staff team. Review of protocol and trial procedures, data entry procedures, problems that may arise and how to prevent them, CGP, safety aspects, IMP accountability and administration, are some of the focusing items.

3.1.4 SUBMISSION PROCESS

During submission process, me and my colleagues provided sponsor, Blueclinical´s "Submission Package", which has a set of documents needed for submission. Sponsor usually requested three main documents: PI CV, protocol page signature by PI and declaration of site conditions. Blueclinical created a template for CV, specific for clinical research focusing in clinical trial experience and GCP training. Declaration of site conditions adapted from Blueclinical involves all head of departments that sign this declaration stating resources, facilities and equipment available for the trial. Other two important documents are requested by CEIC due to position of CRC in the site: declaration signed by Blueclinical authorizing CRC participation in that trial and a declaration from AB, also authorizing CRC participation. This last document is usually signed by our coordinator from the site. Financial agreements are also an important step in submission process, but I will detail it later in this report.

3.1.5 TRIAL RELATED PROCEDURES DURING VISIT

3.1.5.1 Study Visits

Study visits were the most challenging activity performed at site. This was a task that required previous work and organization, in order to get all necessary information, avoiding

protocol deviations. Experience gained over the visits was crucial for my self-confidence in activities performed.

Study visits were prepared in order to be compliant with all the procedures requested by protocol. CRC has an important role in the conduct of study visits. Some tasks were performed in order to achieve complete and correct collection data during visits:

- At least one week before, we checked availability of all necessary materials needed to conduct the visit (e.g. collection kits, necessary material for sending samples, patient questionnaires, if applicable).
- Remembered PI of study visit and the important issues from that visit. In clinical research "what is not written did not happened" and for that reason all must be documented in patient file. Physicians are not used to write everything about the patient in clinical practice routine, and in order to help the doctors with this tasks we made checklists with information that should be written in patient file.
- In the day before we contacted study participant alerting about study visit and reminding to bring the study medication, the patient diary, required fasting or other applicable conditions.
- Previous identification of information and data to be collected during the period patient is at site. We carefully read the protocol section that explains procedures performed in each visit. Besides that, prior knowledge of the information required in the CRF for that visit minimizes faults of information filled in the source document completed on the day of visit such as patient file.

3.1.5.2 Documents

During internship, at site, I had to use several documents. Below I will describe the most important ones.

Protocol is the cornerstone for the conduction of clinical studies. It describes rationale, objectives, design, methods, statistical methods and organization of the trial. Before any study visit, protocol was reviewed in order that visits were compliant with all procedures requested by protocol.

During the trial a large number of documents is generated. Some documents are in TMF before the trial begins, while others are added during and after the trial. During Internship I was also responsible for maintaining TMF updated. It is very important to control versions of documents to understand what version is currently in use.

Informed consent consists of two documents: information sheet and consent form. Informed consent must be signed before any trial related procedure is conducted. It contains information about the purpose of the trial, entry criteria, trials procedures and possible risks. It must be written in Portuguese and in a language understood by the average subjects. Patient should be given time to read information sheet and to discuss all doubts with PI, trial staff, and/or discuss it with family before entering in the trial. Two copies are provided to patient and he should sign both if he accepts to participate in the trial. PI also signs. One copy is returned to the patient and the other is archived in TMF. This was an item many times checked during monitoring visits.

Source documents are all documents that contain source data. Examples are medical records, laboratory reports, subject's diaries, pharmacy dispensing records, and radiographs. These documents are important during monitoring visits allowing monitor to confirm data collected in CRF.

3.1.5.3 IXRS

IXRS (Interactive Voice/ Web Response System) is an useful system, improving inventory management and facilitating blinding procedures**.** For every study visits I had to contact with IXRS. IXRS can be IVRS (Interactive Voice Response System) or IWRS (Interactive Web Response System). To use IXRS I must dial phone number or enter web platform. In ULSM I used both systems. After entering the system I had to confirm patient number, date of birth and visit performed. Subsequently medications codes were provided and a confirmation e-mail was sent to study team.

3.1.5.4 Biological sample Processing

Most visits require urine and/or blood samples collection. Central laboratories are increasingly used as they can ensure standard methods and reduce variations among sites. Besides that, they send results to main database reducing transcription errors. However, in some trials the speed of local results is essential. Usually, when a central laboratory is used, an adequate package for samples and delivery of samples is provided. International Air Transport Association for transportation rules for biologic samples need to be followed and site staff responsible for packaging samples requires appropriate certified training. Although I did not need to process and pack biological samples, me and my colleagues completed appropriate e-learning training.

3.1.5.5 CRF completion

CRF may be electronic or in paper. I only had opportunity to use electronic CRFs. Electronic data entry is the process of entering data directly into a computer database, and has advantages over the paper, like reminders for missing responses, and for inconsistencies found or invalid data. Each user (PI, study coordinator or other appropriate element of study team) has a username and a password associated, so that all data entry and changes performed can be easily traced. Usually I completed CRF in the same day or on the day after the visit. In cases where some information was missing I asked the PI to make patients files amendments in the same day or day after so everything in the CRF could be checked against source documents.

3.1.6 MONITORING

It is sponsor´s responsibility that trials are monitored. A monitor acts as a quality control supervisor that usually monitors the same trial at different sites. Monitor is the link between the site and the sponsor. He makes regular visits to the site that should be scheduled, so that staff team can dedicate some time to answer monitor´s questions and to correct possible mistakes in CRF.

During monitoring visits, monitor usually checks: accuracy and completeness of data entry, eligibility of the patient, concomitant illness and medication properly documented, informed consent properly signed and dated before any study related procedure.

During my internship I assisted to some monitoring visits. I usually requested patient files for monitor verification and assured the CRF was complete. During monitoring visits monitor helped to solve some pending queries in CRF.

3.2 EXPERIENCE AT BLUECLINICAL BACK OFFICE

During my experience at Blueclinical Back Office main activities performed were database organization, contract negotiation and payment management. Each task will be described in more detail in the next sections. One more section is included for others tasks performed during my internship.

Changing from site, as CRC, to Back Office was a great challenge that Blueclinical proposed me. Company´s growth started to request that some specific tasks were centralized and, allocated for a specific person. Physical location of the sites and dispersed information was a barrier for Blueclinical development.

3.2.1 DATABASE ORGANIZATION

First task performed assuming new functions was database organization. All studies from all sites were organized by sponsor and protocol. For each protocol an obsolete paste was created for all obsolete versions of protocol or financial agreements. Protocols were organized by version and date of approval and contracts ordered by Clinical Trial Agreement (CTA) or Financial Agreement (FA). In case of draft versions, indicating the draft number and reviewed by whom (B- Blueclinical, S- Sponsor) and in case of final contract indicating the word final and signature date.

Besides database organization, I also had to group information of all study visits performed in the different sites and about the recruitment status of patients for all studies. This information was obtained from each study coordinator at site.

Main difficulties felt during this task was some missing information as study protocols, or signed financial agreements, which were overcome requesting monitors of the studies the missing documents.

3.2.2 CLINICAL TRIAL AGREEMENT NEGOTIATION

According to article 13 of Law 21/2014, 16th April 2014, the sponsor or his authorized representative shall carry out a financial agreement with the site for the conduct of research activities.

Clinical trial business is very competitive. Despite the strong competition it is important that site evaluates CTA and budget given, before accepting all studies proposed. In many cases, CTA are an overlooked step, considered as time consuming, boring and unnecessary. The budget of a financial agreement can only be considered valid and accepted, if not harmful to the hospital, thus it is very important to review CTA.

CTA negotiation began to be made centrally by me with the support of Doctor Cristina Lopes, and started to be my main task during internship. This is an activity that used to be made individually by each study coordinator at site. CTA negotiation centralization improved efficiency of the company, becoming more consistent and focused in contract revision. Having a person allocated to this task resulted in:

- More consistent approach of CTA negotiation;
- Prevention of work duplication (the same contract is reviewed only once, even if submitted in more sites, only being necessary adaption to the particularities of each site);
- Easier contact with the sponsor (sponsor knows that company has a PC allocated for contract negotiation).

After site qualification sponsor contacts site and/or Blueclinical Back Office to obtain information required for contract completion:

- How contract revision is performed;
- If site has a specific contract for financial protocol;
- Site general budget split;
- Research team allocated to the study;

- Complementary Means of Diagnostic and Therapeutic (CMDT) made locally at site or at central laboratory;
- Site submission process (e.g. parallel submission is allowed);
- The procedures for reimbursement of patient expenses.

Usually, during contract negotiation, sponsor presents two documents:

- CTA - More dedicated to include general and legal clauses.
- FA - More dedicated to financial aspects. Either sponsor´s specific draft or site´s template may be used. Blueclinical has partnership with two sites that have their own financial protocol template. In most cases, financial protocol is incorporated as an annex in CTA.

For CTA review and negotiation it is important to consider applicable legislation described below:

- Law 21/2014, 16th April 2014 - Clinical research investigation Law (15);
- Ordinance nº20/2014, 29th January 2014 - Table of prices charged by National Health System (35);
- Ordinance 306 A/2011 de 20th December 2011 - Value of moderating fees (36);
- Announcement nº1/2015 - Updates moderating fees values (37);
- Decree Law nº113/2011 de 29th November, 2011- Moderating fees-special regimens of exemption or reimbursement (38).
- Decree Law nº128/2012 de 21th June 2012 -First change to Decree Law nº113/2011 (39).

One of the most important steps during this task is clinical trial budget evaluation. It is crucial to consider all the work associated with the study, which is not limited to study visits or tests and materials spent.

Costs pre-study	- Protocol review - Site initiation - Site qualification - Site pre-screening activities - Training of study staff - Pre-study visit - Qualification visit - Attendance to investigator meetings - Organization of initiation meeting - Submission work
Costs during study	- Screening - Subjects enrollment - Subject visits and procedures - CRF completion - Query resolution - Study inspections, audits and monitoring
Costs post-study	- Study close-out - Archiving

Table 3 - Examples of activities that can generate costs in a clinical trial. Adapted (40).

It is critical to consider time spent in pre-study, during study and post study as budget is expected to cover all expenses arising from the study. In Table 3 are described some examples of activities that can generate costs during a trial and that should be taken into consideration (40).

Contract negotiation performed within Blueclinical CRP requires input of various stakeholders:

- Sponsor/ CRO;
- Blueclinical Back Office;
- PI;
- CRC;
- PC.

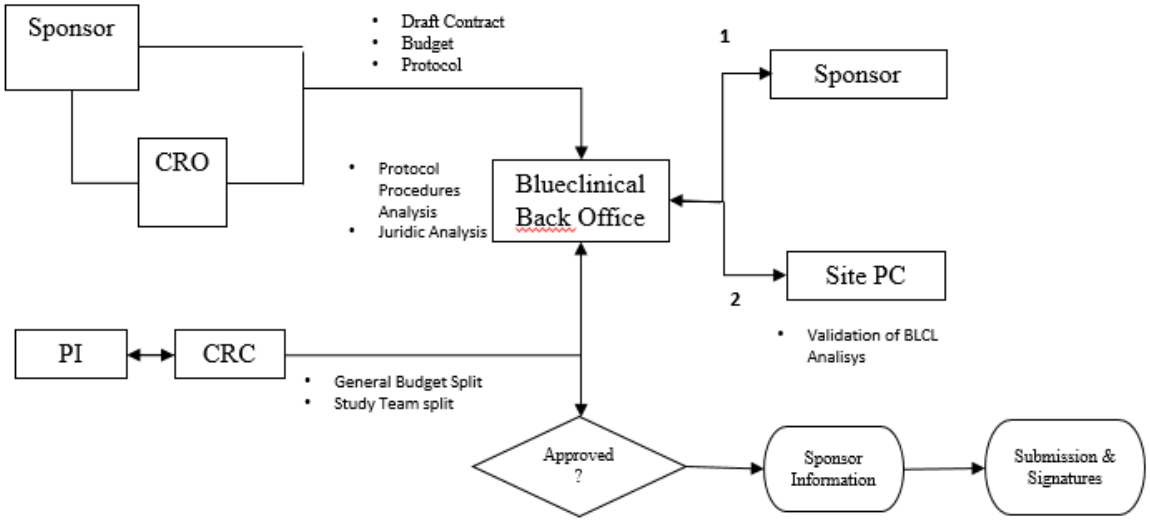

Figure 9 - Blueclinical Flowchart for Contract Negotiation.
CRC-Clinical Research Coordinator; **CRO** - Contract Research Organization; **PC**- Person of Contact; **PI** - Principal Investigator.

Figure 9 describes sequential steps during contract negotiation. After site qualification, I usually requested sponsor/ CRO**,** documents for CTA review, which may include:

- Protocol;
- Detailed Budget;
- CRF blank (it is important to check CRF as it can be very lengthy and complicated, or have a lot of scales);
- Laboratory manual (may be requested to understand the circuit and specific needs to deal with samples).

Schedule of assessments is a great summary of study requirements. It is important to assess number and complexity of scheduled visits and all itens described in protocol that will generate costs. Based on scheduled of assessments I created an excel spreadsheet template to estimate costs associated. CRC allocated at site, gave me, through PI, information about budget split. Contract is reviewed and sent to Sponsor until a final version is reached. Some sites require site revision and in those cases, after a final version is achieved with the sponsor, I send CTA for site PC. After reaching a final version, contract can be signed by sponsor, an then by site and PI and/or Blueclinical.

During contract negotiation I had to daily fullfill a document called “Contract Registration”. Here I had to register:

- Dates of reception and sending of contracts;
- Causes for delay (L-Legal, F- Financial, G- General);
- Responsible for delays (S-site, B- Blueclinical, S- Sponsor).

Blueclinical has a checklist to help reviewing CTA. This checklist is mainly divided in general clauses, recruitment, supply, payments and other important clauses.

3.2.2.1 General Clauses

General clauses are related to items that must be in the contract, for example, the identification of the involved parts, scope of contract, identification of PI, terms and termination of contract, effective date and responsabilities from involved parts. I always checked the presence of these itens in the contract. If not present I requested to add this information.
Depending on the site two options are available in terms of CTA: tripartite (sponsor, site, PI) or quadripartite (sponsor, site, PI and Blueclinical).

3.2.2.2 Recruitment

The itens on the checklist related to the recruiment are the number of participants to be enrolled in the study and end date of recruitment. The information related to the recruiment is relevant for site as amount of effort required to initiate a new protocol varies little with the number of patients that should be enrolled. Effort and time of initiating a trial should be considered and evaluated versus the profit margin per patient. It is important to distinguish between fixed costs or up front costs and variable costs. The first ones, are costs needed for study conduct and are incurred whether or not, a subject is enrolled. Sometimes sponsor requested not to put in CTA the end date of recruitment to avoid the need of an amendment to contract, in case timeline is modified. Expected number of enrolled participants is important as it helps Blueclinical to plan invoicement.

3.2.2.3 Study Materials

CTA should contain information about study materials, including supply, compassionate use, destruction and equipment.

Sponsor should freely supply the site with study drug, comparator, placebo and materials needed to perform the study (patient diary, filters, saline solutions, rescue medication), CRFs or access to data capture system. Reviewing protocol helped me to identify all materials needed, in order to request sponsor for supply or reimbursement of these items. After completion of trial, I tried to negotiate with sponsor that, if applicable, marketed unused study materials that were in perfect conditions, were donated to site for use in standard practice.

According to national legislation after the end of the trial sponsor should provide study participants with study drug for as long as conditions described below are meet: study drug is still not marketed, has proven to be safe and efficacious for the study participant, PI considers that study drug supply is clinically important to the study participant and there are no comparable therapeutic alternatives in terms of safety and efficacy to the study drug. This is called compassive use. When applicable, I requested this information to be included in the contract.

After conclusion of the study or termination of the agreement, used and unused study materials, could either be returned to the sponsor or destroyed at site. Upon sponsor request site may dispose study materials. There are specific cases that require site disposal, like hazardous material, that should be destroyed at site, according to site normal procedures for hazardous material handling. e.g., cisplatin. In case destruction is performed in the site , I usually requested sponsor to pay a fee for the costs incurred with study material disposal. Site should keep appropriate records to document destruction, and destruction should comply with applicable legislation.

Site is responsible for having all equipment available at site ready. In specific cases sponsor may agree to provide site some equipment. Ideally, equipment provided by the sponsor should be described in financial agreement. Unless otherwise agreed in writing equipment should be returned to the sponsor at the end of the trial and site is responsible for using equipment according to instructions, and for its appropriate maintenance and calibration.

3.2.2.4 Payments

In contract revision it is helpful to separate between costs site will incur with staff (direct costs) and costs with equipment and materials (indirect costs). National legislation specifies that direct and indirect costs should be clearly stated in CTA and/ or FA.

Direct costs are costs intended to compensate study staff for their work during the trial. It includes study visits related work and study related fees. Study staff includes PI, sub investigator, nurses and study coordinators, among others. In assessment of direct costs it is important to estimate time needed for scheduled visits, staffing needs for study duration, recruitment effort needed, time spent in conference calls, e-mails, CRF completation, reporting SAEs, monitoring visits and shipping samples. Payment of study staff has to take into account not only value/ hour, but also, vacations, increased salaries (depending on duration of study). CTA and/or FA should identify in an individual basis and function performed, the remuneration of the researcher and the other team members. Direct costs may also include the following fees:

- Start up fee - fee to compensate for administrative work needed to start the study. This payment intends to pay, but is not limited to, protocol-related training requirements, submission for approval by AB and getting all site documents needed for study submission to regulatory authorities. This amount should be paid after the signature of the agreement. This fee may be given or negotiated by the site. I always try that these fees are non-refundable and apart from patient enrollment fee.
- Coordinating Investigator fee - this fee intends to pay for work of investigators in case national coordinator is from that site.
- Close-out fee - this fee intends to pay for administrative work with site close-out activities and archive maintenance.

Indirect costs include consultations, CMTD, patient fees, patient expenses and unscheduled hospitalization. CTA and/ or FA should clearly state all the procedures performed during the trial. Consultations and CMTD related costs should be detailed indicating National Health System (NHS) code, price of item performed, patient fee, number of times the item is performed and total value. Listing all the procedures performed during the study shows the

indirect costs site will incur with consulations, and laboratory testing. Price established in CTA and/or FA, cannot be lower than price established in NHS table.
Sometimes, protocol requires exams, which by their specificity, may not be available in all sites or the site cannot guarantee they are performed according to protocol schedule of exams. This information should be clearly stated in CTA and/ or FA and a description should be made of what will be performed at site and what will not.

The expected gain for a study participant is in health gain and not material. However, participation in clinical trials may result in costs and economic losses to its participants, so it is fair to reimburse any losses suffered by the participants arising from their participation in clinical trials as lost wages, travel expenses and food. It is not a benefit or incentive to participate in the clinical trial, but a way to offset the costs of participants. Therefore, sponsor should support costs due to reimbursement or compensation for expenses and damages incurred by study participants and where applicable, by their legal representative. Study participants have to submit the appropriate documentation (e.g., invoice, statement of the employer, proof of social security on how he/she is not receiving any sickness or unemployment benefits) in order to be reimbursed. Expenses are reimbursed by sponsor on a pass-through basis, upon receipt of an original itemized invoice, and site is responsible for delivering to study participant the amounts due to expenses reimbursement (41).

Study participants may need to perform for safety reasons due to their participation in the study, unscheduled visits or more procedures than originally planned by the protocol when such activities become essential due to a change in the patient's clinical status (e.g. on the occurrence of an adverse event or serious adverse event). In case adverse event is considered probably related with study drug, sponsor/ CRO should be responsible for this payment, and this information should be part of CTA and/or FA.

According to national law, remuneration of PI and research team is allowed. In case PI and research team are NHS workers, payments are made through institution (15). This is applicable for all institutions with whom Blueclinical works for. In the case of tripartite agreements there is only one payee (institution), while in the case of quadripartite agreement there will be 2 payees (institution and Blueclinical receiving their share directly from sponsor). General budget distribution must also be included in CTA and/or FA. This varies among the institutions, that choose the best way to make their budget distribution. Apart

from that, distribution should be individualized between research team. Advanced payments **(**like start up fees) should be stated as well as payment schedule and payment method. Usually, sites complain they wait a long time to receive money from research companies. I always requested for a quarterly payment so the site and research team can be motivated. Usually payments performed are made by bank transfer, so it is important to state the bank details in the CTA and/or FA. Usually I request sponsor to use a simple denomination for bank transference: name of the responsability center - protocol code - payment period and parcel. This will help to identify what visits are being paid.

3.2.2.5 Other Important clauses

Other important clauses that should be present in a CTA are: monitoring, audits, inspections, safety information, archive, civil responsibility (according to article 15º from national law, sponsor has to get an insurance intended to cover civil responsibility), confidentiality, intellectual property, publications and force majeure.

During contract negotiation I was able to identify several challenging itens, namely:

- Start up fees;
- Procedures called standard of care;
- Reimbursement of salary losses;
- Unscheduled visits and unscheduled hospitalizations;
- Compassionate use of study drug.

These were mainly solved by the following activities:

- PI interview and staff team to determine procedures standard of care;
- Invoicing unscheduled events as passthrough costs (e.g hospitalization).

3.2.3 PAYMENT MANAGEMENT

Sites usually complain about slow payments and reimbursements. It is extremely important to manage receivables in order to collect all it is owned to site.
It is important to keep track of payments: know what needs to be invoiced, and when, as per contract. This was my main responsibility. First task performed was asking my colleagues

all information they had about payments. I had to group information on payments performed to the site, site´s invoice number and date of payment. Some sites had this information more or less organized, while others did not. Then, I contacted sponsor, in order to get the most accurate information on payments already performed to site. I did this for all sites and for all studies. Actively seeking information from the sponsors created some constrains, but easily overcome.

CRC at site, had to complete a map of weekly activities and I was responsible for gathering this information in a database. This database allowed me to maintain control over payments due to sites.

When I am reconciling payments, payment detail is requested when not provided and all discrepances are clarified with the sponsor.

3.3 OTHER ACTIVITIES

3.3.1 QUESTIONNAIRES OF INTERESTS

Questionnaires of Interests are a strategic tool for the development of Blueclinical CRP. It is an electronic questionnaire that has two main objectives:

- Understand who are the physicians interested in performing clinical research in Portugal;
- Understand their areas of interest.

This questionnaire has a list of all possible clinical pathologies that physicians will have to choose. This will help to characterize which are the main interests of our physicians in Portugal and Blueclinical can proactively search for new projects to Blueclinical CRP network. Physicians were requested to respond via an electronic questionnaire. While at ULSM, I had opportunity to collaborate in collecting this information.

3.3.2 QUALITY SYSTEM

A Quality Management System (QMS) is a formalized system that documents structure and responsibilities to achieve quality management (managing a process to achieve maximum customer satisfaction at the lowest cost while continuing to improve process). QMS makes

an organization more process oriented, customer focuses and with the ability to do everything better, thus giving an organization, competitive advantage.

Quality manual is an official document where companies detail how QMS operates. The format and structure of the manual will depend on company´s size and complexity. A quality manual usually has: company organization, company mission, vision, values, company code of conduct and quality policy.

A Standard Operating Procedure (SOP) is a set of guidelines used consistently to dictate a set of actions performed in a given situation. An effective SOP template allows to build uniform work instructions that are linked to some type of design, development or assessment tools. These instructions promote consistency, structure and control in the workplace and they meet regulatory requirements of the relevant governing body. SOPs have to give specific information such as who will perform the task, what materials are necessary, where the task will take place, when the task shall be performed and how the person will execute the task. To achieve consistency and structure, processes must be put in place to ensure that SOPs are in writing, consistently formatted, reviewed regularly, approved by management, version controlled, indexed, used regularly, archived and document controlled.

QMS can bring competitive advantage to a company. All employees of a company make part of the QMS that is everyone´s responsibility.

During my internship I produced two SOPs: Contract Negotiation and Invoicing Control.

3.3.3 TRAINING

During my training I had opportunity to perform e-learning and face-to-face training. All the training performed was recorded in a training log sheet that has a template created by Blueclinical.
Contract negotiation, pharmacovigilance, and project management are examples of some issues where I had face-to-face training. I also performed some self-study sessions e-learning (GCP, adverse events reporting, informed consent) and some webinar sessions mainly related with clinical trial budget and clinical trial agreements.
During internship I had opportunity to complete CLIC level 1. CLIC arose from the need to improve clinical research training in Europe, in order to make Europe more competitive,

with qualified healthcare professionals. It is extremely important that healthcare professionals have access to a specific training adapted to the current requirements of clinical research. CLIC is a free training available in e-learning format. It is a flexible course, suitable for healthcare professional needs. CLIC is created through the cooperation of two entities: Pharma train (training for the development of new medicines, in which clinical trials are critical) and Ecrin (infrastructure dedicated to academic research and studies from researcher's initiative). The first version was implemented in March 2013 and the Portuguese version was available in June 2014.

CLIC has three different levels: level 1, dedicated to sub-investigators and non-medical staff (16 hours), level 2 dedicated to PI (additional 24 hours) and level 3 in case PI is simultaneously sponsor (additional 24 hours).

4 DISCUSSION

My internship was linked to a Hospital (site) and to Blueclinical Back Office, which gave me the opportunity to see two different realities that complement themselves. During this period I had opportunity to perform diversified tasks. This learning model that integrates an internship in the second year of the master, proved to be efficacious, as it helped me to consolidate all I learned in the first year of the master.

I am a pharmacist and I have worked 9 years in a pharmacy, but environment is completely different so I believe I felt the same difficulties that my younger colleagues felt during internship. This was challenging as it was a new area for me where I did not felt comfortable. This curricular training contributed to my experience and for the development of my hard and soft skills. Professional market is increasingly seeking professionals with social competence and communication (soft skills). In clinical research, soft skills are extremely important as they improve the relationship and communication with all involved stakeholders: study team, colleagues, pharmaceutical industry (clients) or our supervisors.

During this period I have learned how to deal with the unexpected and to solve problems, always looking for the better solution. Experience at site, although being short, was very rewarding. It was my first experience in clinical research world and gave me opportunity to understand the different steps that a trial goes through, within a site. CRC works with research study team under the direction of PI. PI is the ultimate responsible for the conduct and management of the study but CRC supports, facilitates and coordinates daily activities playing an important role at the site.

Main constrains experienced as CRC were to get responses of physicians for feasibilities, or the constant lack of availability of physicians to spend time with CRC for signatures, or papers needed for submission. I think that difficulties felt at the beginning improved over the time as physicians have gained confidence in CRC team. Strategies used to overcome this problems were helping the physician to fulfill feasibilities as there are some specific questions about facilities that CRC could answer.

Study visits were always difficult to perform as I was not used to it. With experience I understood that a good preparation was the key for success of study visits. A good knowledge of procedures requested by protocol and CRF was crucial. If I was well prepared I felt much more confident that anything would miss.

In clinical research, study procedures must be strictly followed. I have learned that "what is not written does not exist", so, it is important to be rigorous in the tasks performed. It also helped me to think in monitor point of view, what they would like to check. Information in CRF, had to be in a source document. For example if physical exam of patient was normal, I could not assume it was normal just because PI did not wrote anything in patient file. In this case it had to be written "Physical examination- normal".

Reading and understanding a study protocol was challenging and a difficult task, mainly because of unawareness of its organization and the use of specific terms. This was a task that I think I improved a lot with practice as I overcome language barrier of some specific terms and I get used to protocol organization, learning where to look for further information. Some protocols, are extremely complex, like in oncology, but with practice, I have learned to understand it. Good English knowledge is crucial in this area that I think that I have improved.

Other big difficult felt was time management. We always deal with deadlines to perform our tasks and I was not used to it. This was also improved, since as we do different tasks, we gain experience, making it better and quicker, thus being more efficient.

Blueclinical encourages me and my colleagues to be autonomous which can be scary at the beginning, but contributes a lot for our growth. We cannot learn if we just see the others doing the tasks or if we are always asking what we should do. The support is important, but autonomy is essential for our growth.

During internship I helped on submissions, but I had not the opportunity to make submissions alone and I did not had opportunity to make any reporting of adverse events or serious adverse events. The main reason was because of the short time performing functions as CRC.

In Blueclinical Back Office, being responsible for contract revision, gave me opportunity to work with different sponsors and obliged me to work with different people and documents, so I had to adapt myself. Also, improvement of communication skills became visible. Communication became clearer, shorter, and objective and I started to justify and argue my point of view during contract negotiating. At first, I had some constrains with CRO and pharmaceutical companies. Now, I feel most of these constraints with industry were totally overcome as it is in the best interest of all parties, because the quicker the submission is, the quicker the study and recruitment can start.

Writing SOPs was a challenging activity as I had never written one. This task was performed at the end of my internship and I believe I performed it in the right time. I already had some experience in the tasks performed, and I did not felt it was difficult. I believe the best advice I had before writing it was "try to detail your activities the way you think the process should ideally always occur". That's what I did, and I believe I was successful.

Major personal competences developed were:

- Autonomy;
- Responsibility;
- Time Management;
- Conflict resolution;
- Ability to set priorities, planning and coordination of multi-tasking skill;
- Team work among different healthcare professionals;
- Problem solving;
- Priority management;
- Assertiveness.

Major technical competences developed were:

- Deep understanding of legislation and guidelines applicable for clinical research;
- Medical and scientific terminology;
- Knowledge of the various stages of a study in a clinical trial site;
- Protocols comprehension;
- Financial agreements review;
- Development tools for payment tracking;
- Understanding quality manual system.

I am grateful for the responsibilities and opportunities that Blueclinical provided me during internship.

5 CONCLUSION

This training model proved to be efficacious to me, as it helped me to consolidate all I had learned in the first year of the master. The background obtained in the first years was determinant to successfully conduct the assigned tasks.

This curricular training contributed to my experience and for the development of my skills. Besides using and consolidating academic background from the master it gave me a good insight of marketplace, providing me a good vision of the Pharmaceutical Industry and clinical research. During this period I had opportunity to perform different tasks, and I felt several difficulties as already explained but I think I could overcome them. This internship, helped me to learn with acquired experience, in a daily basis. In all difficulties and obstacles I encountered during this stage, I also I found an opportunity for growth and improvement, taking advantage of daily experiences to do better in future.

I believe the objectives proposed for this 9 month internship were successfully accomplished.

6 BIBLIOGRAFY

1. Blueclinical. Quality Manual. 2014.

2. R&D consultancy [Internet]. [cited 2015 Jan 2]. Available from: http://www.blueclinical.pt/consultancy/en/

3. Blueclinical. Blueclinical Phase I [Internet]. [cited 2015 Jan 2]. Available from: https://www.blueclinical.com/pt/

4. Blueclinical. Blueclinical Clinical Research Partnership [Internet]. [cited 2015 Jan 2]. Available from: http://www.blueclinical.pt/crp/pt/

5. Blueclinical. Protocolo de colaboração entre a Unidade Local de Saúde de Matosinhos e a Blueclinical-Investigação e Desenvolvimento em Saúde. 2013.

6. ULSM. Unidade Local de saúde de Matosinhos [Internet]. [cited 2015 Jan 7]. Available from: http://www.ulsm.min-saude.pt/content.aspx?menuid=5

7. Blueclinical. Implementação do Protocolo de colaboração entre ULSM e Blueclinical. 2013.

8. EMA. About us [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid=

9. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical research involving human subjects. 2013.

10. Griffin J, Posner J, R.Barker G. The Textbook of Pharmaceutical Medicine. 7th ed. Wiley-Blackwell; 2013.

11. Edwars L, Fletcher A, Fox A, Stonier P. Principles and Practice of Pharmaceutical Medicine. 2nd ed. John Wiley & Sons; 2007.

12. International Conference on Harmonization. Guideline for Good Clinical Practice E6 (R1) [Internet]. 1996. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

13. International Conference on Harmonization. Addendum Good Clinical Practice- E6 (R2) [Internet]. 2014. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Concept_Paper_July_2014.pdf

14. Directive 2001/20/ CE of the European Parliament and of the council of 4 April 2001 [Internet]. Official Journal European Communities; 2001. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

15. Assembleia da República. Lei nº21/2014 de 16 de Abril. Diário da República. 2014.

16. Comission Directive 2005/28/EC of 8 April 2005 [Internet]. Official Journal of European Communities; 2005. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

17. Proposal for a Regulation of European Parliament and of council [Internet]. 2012. Available from: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

18. Regulation (EU) Nº 536/2014 of the European Parliament and of the council of 16 April 2014 [Internet]. Official Journal European Communities; 2014. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

19. Apifarma. Ensaios Clínicos em Portugal [Internet]. 2013. Available from: http://www.aibili.pt/ficheiros/EstudoInvestigClinica_em_Portugal_jun2013vf.pdf

20. Beaumont H. Regulamentação nacional aplicável a medicamentos. 2014.

21. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov [Internet]. 2010 Mar [cited 2015 Feb 12];9(3):203–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20168317

22. International Conference on Harmonization. E8-General Considerations for Clinical Trials [Internet]. 1997. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf

23. Carlson MDA, Morrison RS. Study design, precision, and validity in observational studies. J Palliat Med [Internet]. 2009 Jan [cited 2015 Jan 29];12(1):77–82. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2920077&tool=pmcentrez&rendertype=abstract

24. Regulation (EC) Nº 141/2000 of the European Parliament and of the council of 16 December 1999. [Internet]. Official Journal European Communities; 2000. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

25. FDA. Guidance for Industry - Adaptative Design clinical trials for Drugs and Biologics. [Internet]. 2010. Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf

26. IMI. Strategic Research Agenda [Internet]. [cited 2015 Feb 12]. Available from: http://www.imi.europa.eu/content/research-agenda

27. FDA. Critical Path Opportunities Report [Internet]. 2006 [cited 2015 Mar 20]. Available from: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf

28. EMA. Paediatric medicine [Internet]. [cited 2015 Apr 3]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp

29. EMA. Roadmap to 2015 [Internet]. 2011 [cited 2015 Mar 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf

30. FDA. Critical Paths Opportunities Report [Internet]. 2006. Available from: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf

31. U.S. National Institutes of Health. ClinicalTrials.gov [Internet]. [cited 2015 Mar 10]. Available from: https://clinicaltrials.gov/ct2/home

32. Soares N. Inovação em contraciclo [Internet]. 2013. Available from: https://www.blueclinical.com/pt/artigo.php?type=1&id=1

33. Infarmed. Estatísticas de avaliação de Ensaios Clínicos pelo Infarmed [Internet]. 2014 [cited 2015 Apr 3]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS

34. Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspect Clin Res [Internet]. 2010 Jul [cited 2015 Mar 22];1(3):106–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3146075&tool=pmcentrez&rendertype=abstract

35. Assembleia da República. Portaria nº20/2014, 29 de Janeiro. Diário da República. 2014.

36. Assembleia da República. Portaria 306A/2011, 20 de Dezembro 2011. Diário Da República; 2011.

37. Administração Central do Sistema de Saúde. Circular Normativa nº1/2015, 15 de Janeiro 2015. 2015.

38. Assembleia da República. Decreto-Lei nº 113/2014, 29 de Novembro 2011. Diário Da República; 2011.

39. Assembleia da República. Decreto-Lei nº128/2012, 21 de Junho 2012. Diário Da República; 2012.

40. Williams D. Negotiating Clinical Trial Budget. 2011.

41. CEIC. Documento Orientador-"Sobre o pagamento a participantes em ensaios clínicos" [Internet]. 2011. Available from: http://www.ceic.pt/portal/page/portal/CEIC/Documentos/DOCUMENTOS_CEIC/DOCUMENTOS_APROVADOS/Microsoft Word - Documento2.pdf