Universidade de Aveiro Secção Autónoma das Ciências da Saúde

2014

DIANA FILIPA GOMES LEITE

ESTÁGIO CURRICULAR NUMA UNIDADE DE ENSAIOS CLÍNICOS DE FASE I

CURRICULAR TRAINING AT A PHASE I CLINICAL TRIALS UNIT

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Relatório apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Professora Doutora Maria Joana da Costa Gomes da Silva, Professora adjunta da Universidade de Aveiro e da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical Lda.

Dedico este trabalho ao meu noivo e à minha família, por serem o meu porto seguro.

o júri

Presidente	Professor Doutor José Luís de Almeida Professor Associado Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro
Arguente	Professor Doutor Bruno Miguel Alves Fernandes do Gago Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro
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agradecimentos

No final de uma etapa tão importante da minha vida, e consequentemente o início de outra ainda mais aliciante, não poderia deixar de agradecer a todos os que me acompanharam e me apoiaram ao longo desta caminhada, em especial:
Ao Professor Doutor Luís Almeida pela oportunidade de estágio na Blueclinical e pela confiança em mim depositada. Um agradecimento especial pela sua sabedoria e motivação transmitidas desde a licenciatura.
À Professora Doutora Joana Silva pela orientação, conselhos e crítica revisão a este relatório.
Ao Professor Doutor Bruno Gago, por toda a sua dedicação ao Mestrado em Biomedicina Farmacêutica e pela motivação transmitida aos seus alunos.
À Doutora Cristina Lopes por tanto me ter ensinado, bem como pela sua garra e dedicação à Blueclinical e aos seus colaboradores.
À Dra. Benedita Pereira por ter acompanhado os meus primeiros passos no estágio bem de perto e pela confiança transmitida.
A toda equipa Blueclinical, especialmente às meninas da Fase I, Gisela, Diana Pádua, Diana Santos e Paula pela amizade e espírito de interajuda. Somos a prova de que "a união faz a força".

À Catarina Morais por estar sempre presente, e principalmente por ser uma melhor amiga para a vida.
Ao Cardoso, à Daniela, Bárbara e Andreia, por termos crescido juntos e por terem dado uma cor especial ao meu percurso académico.
À Jessi, irmã do coração, pois nem o tempo nem a distância física que nos separa deteriora a nossa amizade e cumplicidade.

Aos meus pais, pelo apoio incondicional. Ao meu irmão, cunhada e afilhada Sofia por me transmitirem calor no olhar. A toda a minha família, especialmente primos e madrinha por me terem transmitido a importância da família e me encherem de amor.
Aos meus sogros, por todo o carinho e força que me transmitem. Aos meus cunhadinhos e sobrinho Santiago por juntos solidificarmos a família Domingues.
Ao meu noivo, quase esposo Michael, por todos os dias me mostrar o significado da palavra *Amor,* fazendo de mim a mulher mais feliz do mundo. Amo-te muito!

palavras-chave

Ensaio clínicos, Fase I, Bioequivalência, Biodisponibilidade, Voluntários saudáveis, Assistente de ensaio clínico

resumo

Este relatório descreve o estágio curricular numa Unidade de Ensaios Clínicos de Fase I, Blueclinical Lda, empresa com diferentes áreas de negócio em investigação clínica.

Tendo em conta a investigação clínica, é apresentado uma visão geral do tradicional e do novo paradigma de desenvolvimento farmacêutico, bem como informação detalhada sobre ensaios clínicos de Fase I e de Bioequivalência, e sobre o ambiente regulamentar Europeu e Português.

Durante o período de estágio, participei em nove submissões de ensaio clínico às Autoridades Competentes nacionais. Participei também na condução de cinco ensaios de bioequivalência / biodisponibilidade em voluntários saudáveis, nos quais desenvolvi competências como assistente de ensaio clínico e gestora de projeto. Realizei atividades complementares noutras áreas de negócio da Blueclinical, como na Escrita Médica e no Sistema de Gestão da Qualidade, que alargaram as minhas competências em outras áreas da investigação clínica. Durante o estágio, senti uma melhoria significativa das minhas capacidades pessoais, nomeadamente na gestão de tarefas, de tempo e na capacidade de comunicação e espírito de liderança em contexto de atividades profissionais.

Este estágio curricular integrado no curso de mestrado, aumentou a minha compreensão dos processos da investigação clínica e perspetivas de oportunidades de trabalho. Também me permitiu identificar áreas de interesse onde quero desenvolver a minha carreira, nomeadamente gestão de projeto.

keywords

Clinical trials, Phase I, Bioequivalence, Bioavailability, Healthy volunteers, Clinical trial assistant

abstract

This report describes a curricular training in a Phase I Clinical Trials Unit, Blueclinical Ltd, company with different business areas in clinical research. Regarding clinical research, an overview of the traditional and the new paradigm of pharmaceutical development is present as well Phase I and Bioequivalence clinical trials details, the European and Portuguese regulatory environment.

During the training, I participated in nine clinical trial submissions to Portuguese Competent Authorities. I also participated in the conduction of five bioequivalence / bioavailability trials in healthy volunteers, in which I developed competences as clinical trial assistant and project manager. I performed complementary activities at the other business units of Blueclinical, such as Medical Writing and in Quality System Management, which broadened my competences in other areas of clinical research. Throughout the internship I felt a substantial improvement of my personal skills, such as time and tasks management and communications and leadership skills in the context of professional activities.

This integrated curricular training in the master course enhanced my understanding of clinical research processes and enlarged my vision of work opportunities. It also allowed me to identify areas of interest that I intend to pursue in order to develop my career namely clinical research project manager.

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LIST OF ABBREVIATIONS

BA	Bioavailability
BE	Bioequivalence
CA	Competent Authority
CEIC	Comissão de Ética para a Investigação Clínica
CNPD	Comissão Nacional de Proteção de Dados
CRF	Case Report Form
CRP	Clinical Research Partnership
CRM	Clinical Research Manager
CTA	Clinical Trial Assistant
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medicine Product
PI	Principal Investigator
PK	Pharmacokinetics
QC	Quality Control
RN	Research Nurse
RP	Research Physician
SD	Source Documents
SOP	Standard Operating Procedure
TMF	Trial Master File

1. INTRODUCTION

This present work consists of my curricular internship report in the scope of the second year of Master's Degree in Pharmaceutical Medicine of University of Aveiro. The second year of this Master Degree is composed by theoretical modules together with an "on-the-job" training, a project or a dissertation writing. Considering these three hypothesis, I have chosen the curricular internship, to obtain professional experience and to put in practice what I had learned in the master course and bachelor of biomedical sciences course.
My curricular internship occurred during 10 months from July 2013 to April 2014 at Blueclinical – *Investigação e Desenvolvimento em Saúde Lda*, here in after referred as Blueclinical, as Clinical Trial Assistant (CTA). CTA was the main job activity that I performed during the internship, however I had the chance to perform other tasks and to acquire experience in areas that do not fall in the job description of a CTA.

This report is organized in the following chapters:

- Introduction: In this chapter it is presented an overview of my characterization of Blueclinical related to mission, facilities and staff. The primary and the secondary objectives proposed for this training are also addressed in this chapter. A state-of-the-art regarding the pharmaceutical research and development, with a special attention to Phase I clinical trials and Bioequivalence (BE) and Bioavailability (BA) studies, due to my specific training experience. State-of-the-art also includes the regulatory environment in the European Union and in Portugal, as well a summary status of clinical trials submissions in Portugal.
- On the job training: In this chapter it is detailed all activities performed during the internship. This chapter distinguished generic training unrelated to Phase I studies, and specific training related to Phase I clinical trials activities;
- Discussion: Here it is analysed the tasks assigned and the difficulties felt in each one. In this chapter is also identified the learning outcomes and the personal competences developed.
- Conclusion: In this chapter it is presented a summary of principal features that arises from internship in Blueclinical.

1.1. VISION OF THE HOST INSTITUTION

Blueclinical – *Investigação e Desenvolvimento em Saúde Lda* is a recently Portuguese company that was officially created in 2012.

This company is divided in three business units: Research & Development Consultancy (R&D), Clinical Research Partnership (CRP) and Phase I. The company organization is schematized in the organogram in Figure 1.

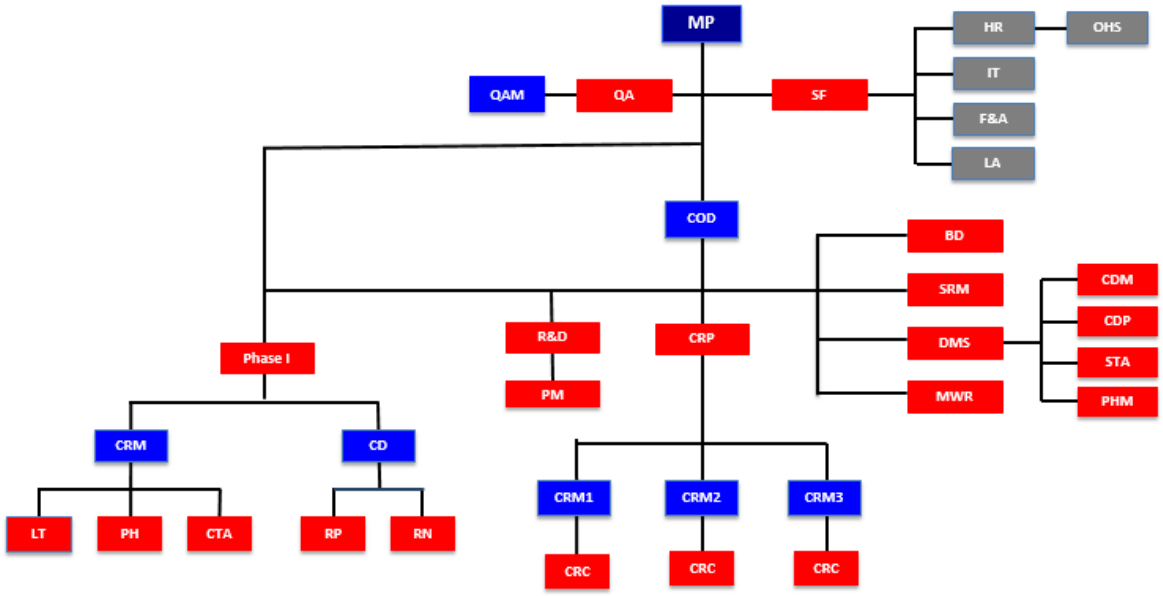

Figure 1 - Blueclinical Organogram(1)

BD-Business Development; **CDM**-Clinical Data Management; **CDP**-Clinical Data Programming; **CD**-Clinical Director; **COD**-Clinical Operations Director; **CRC**-Clinical Research Coordinator; **CRM**-Clinical Research Manager; **CRP**-Clinical Research Partnership; **CTA**-Clinical Trial Assistants; **DMS**-Data Management and Statistics; **F&A**-Finances and Accounting; **HR**-Human Resources; **IT**-Information Technology; **LT**-Laboratory Technicians; **LA**-Legal Affairs; **MP**-Managing Partners; **MWR**-Medical Writing and Reporting; **OHS**-Occupational Health and Safety; **PHM**-Pharmacometrics; **PM**-Project Management; **QAM**-Quality Assurance Manager; **R&D**-Research and Development; **RN**-Research Nurses; **PH**-Research Pharmacy; **RP**-Research Physicians; **SRM**-Safety Risk Management; **STA**-Statistics; **SF**-Support Functions

The mission of Blueclinical R&D is to support other institutions, especially start-ups, in the development of their projects with a view of subsequent commercialization. Among other functions, R&D provides consulting services in non-clinical, clinical, pharmaceutical and regulatory area, and it helps at preparation of development plans of new drugs, medical devices or other health products (2).

Blueclinical CRP was raised to improve the actual situation of clinical research in Portugal, considering the administrative and organizational factors as major limitations of it. The mission of CRP is to support the activity of clinical research sites, by the creation of organized and expert

research teams in order to comply with ethical and quality standards and with all legal requirements. Another goal of CRP is to create a network of clinical research sites, to improve the efficiency of Portuguese sites and to obtain recognized reputation for excellence in clinical research (3).

The mission of Blueclinical Phase I is conduct Phase I clinical trials in healthy volunteers and early proof-of-concept studies in selected populations of patients. Blueclinical Phase I consists of a Human Pharmacology Unit to conduct Phase I clinical trials in healthy volunteers located at the third floor of Prelada's Hospital, Oporto. Blueclinical Phase I has also a partnership with CUF Hospital, Oporto, to conduct early proof-of-concept trials in selected populations of patients (4). Apart from these units, Blueclinical offers other services such as Medical Writing, Data Management and Statistical Analysis (see Figure 1). In this way, Blueclinical is suited to support the entire process of drug or medical devices development.

Phase I unit contains appropriate facilities, qualified collaborators (Figure 1) and the essential clinical and laboratory equipment. At present the clinical team is composed by a Clinical Director, with experience in more than 20 Phase I clinical trials, a Nurse Coordinator, 6 Research Physician (RP) and 9 Research Nurses (RNs). The non-clinical team is constituted by a clinical research manager (CRM), a research pharmacist, a laboratory coordinator, 2 CTAs and 4 laboratory technicians.

Blueclinical Phase I is a 27-bed unit which also contains:

- Seven three-beds rooms and three double bedrooms with private bathroom. The rooms are properly equipped with adjustable beds, furniture and televisions. Each room also contains two windows, one with bars to the outside and another to the corridor. The internal window allows supervision by Blueclinical staff. Each room also contains buttons of emergency call;
- A pharmacy. This room has temperature and humidity control and protection from direct light. The access to this room is restricted and controlled by an electronic system;
- A storage room. Like the pharmacy, this room has protection from direct light, temperature control and restricted access;
- A laboratory room, equipped with appropriated equipment to sample processing;
- A nursing room adequately equipped. It is mostly used to ambulatory sample collection;
- A physician office, also equipped with clinical material. It is used for medical examinations;
- A dining and living room. It contains tables, chairs, couches and a television;
- A private area with volunteers and staff lockers;

- A computer server room. This room has temperature control and protection from direct light and restricted access;
- Private individual showers equipped with an emergency system call;
- A coordination room;
- A management room;
- An emergency cart, available on the corridor;
- Complementary emergency services, provided by Prelada's Hospital;

Phase I Unit contains the required clinical equipment, such as two electrocardiographs, a cardiac defibrillator, twelve thermometers, five blood pressure monitors, a scale (max 200kg) and eight portable watches. The Unit also contains the appropriated laboratory equipment such as two refrigerated centrifuges for blood sample processing, an ultra-freezer (-80ºC), a freezer (-20ºC), a combined refrigerator and freezer (4ºC, -20ºC) with temperature and humidity loggers. All equipment is calibrated or verified by an external company depending on the equipment specification.

Besides the legal requirements and the regulatory guidelines, Blueclinical has its own standard operating procedures (SOP) which cover the three divisions of the company. There are SOPs which are applicable to all three divisions, and there are others that are specific to each division.

1.2. STATE-OF-THE-ART

In this section is presented the key points of drug development, mainly related to the changing paradigm of drug development and the present regulatory environment in Europe and in Portugal.

Development of new drug

The drug development process is a "long path from petri dish to patient", i.e. the whole process since a new molecule is found until the pharmaceutical product is launched into the market. Drug development is a complex and expensive process taking approximately 10 to 15 years for a molecule develop in a medicine with tangible benefits for patients (5).

This process enhanced the number of available therapeutics to the patient, and it increased the condition of public health, for instance the life expectancy and the quality of life (5). However, nowadays, pharmaceutical industry is facing a crisis, i.e. although it has invested more money in pharmaceutical research, the number of new drugs is decreasing (6).

The current paradigm of drug development includes the following steps [adapted from (5,7)]:

- **Pre-discovery**

Drug development starts with the growing understanding of the disease biology; then a "target" (such a protein or gene) that has a role in the disease mechanism is selected.
After target identification, a chemical or natural compound that inhibits or enhances the target activity, has to be identified. Compounds that show the desired effect are called "hits".

- **Drug discovery**

After "hits" identification, additional tests are performed to reduce the number of possible compounds available and to come up with "lead compounds". These lead compounds need chemical improvements to enhance different properties. The desired compounds have to be selective within target disease and can be safely absorbed by the body and with few side effects.

- **Non-clinical studies:**

After the lead compound discovery, additional studies have to be done to better understand the compound behaviour. The non-clinical studies are conducted in animals, cells and computer models to evaluate safety and efficacy of the compound.
If this process is successful these studies will identify a lead compound to be used in clinical trials, and estimate the safe start dose in human's trials.

- **Phase I or Human Pharmacology Clinical trials:**

These trials are conducted in a small number of healthy volunteers (20-100) because the investigational medicinal product (IMP) is tested in people, for the first time. The goals of these trials are to assess tolerance, explore drug metabolism and describe the pharmacokinetic (PK) proprieties. They can be also used to evaluate drug interactions.

- **Phase II or Therapeutic Exploratory Clinical trials:**

These trials are conducted on around 100 to 500 patients with the disease. The objectives are to determine the most effective dosages for the IMP and the most appropriate pharmaceutical form. It is also used to estimate dosage for subsequent studies. Phase II can be divided in IIa (pilot trials designed to assess dose-response, frequency of dosing) and IIb (pivotal trials designed to assess IMP efficacy).

- **Phase III or Therapeutic Confirmatory Clinical trials:**

The goals of these trials are to confirm efficacy, establish dose-response and safety profile and generate data about benefit-risk relationship of the IMP. These trials are conducted in about 1000 to 5000 patients.

- **Market:**

If the information and results from all studies, show the safety and effectiveness of IMP, the authorization of commercialization is given by regulatory agencies. After medicine licensing for use, pricing and reimbursement measures are determined, the medicine starts to be commercialized.

– **Phase IV or Therapeutic Use:**

Even after the medicine approval, it is necessary to conduct trials. The objectives are to refine dosing recommendation, identify less common adverse events and re-evaluate the benefit-risk relationship.

This approach of drug development is slow, complex and expensive. Besides it is time-consuming, there is a considerable possibility of project failure in the last phases, with the lack of efficacy as the main reason for attrition in drug development (6).

Nowadays a new development model was created, considering the negative aspects of the actual approach as improvement opportunities(8). There are two significant differences between the models (Figure 2) (8):

– In the new approach, the molecule development only occurs after an exhaustive study of disease pathophysiology;
– Proof-of-Concept studies are enforced in well-defined patient populations, to establish the safety of drug candidates and explore the relationship between dose and desired function.

Proof-of-Concept studies allow testing a non-clinical hypothesis about mechanism of action and quickly demonstrate the therapeutic benefit to patients. Thereby if IMP fails in the beginning of the process, it prevents failures that cost a millions (8).

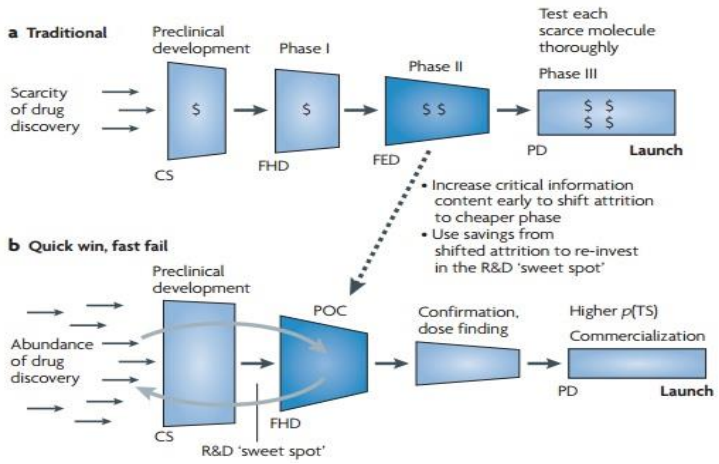

Figure 2- Traditional paradigm versus new paradigm of drug development steps(8)

Other actual challenge in Pharmaceutical industry is innovation. There are exist unmet medical needs and the number of new molecules entities is low (9). The productivity challenge requires a more collaborative approach between academy and industry, to identify breakthroughs in basic research that may translate into clinical development opportunities (9). Usually pharmaceutical industry has the entire responsibility of the process – they fully fund and reap all commercial

benefit. In the new collaboration model, there are external collaborations and outsourcing, so development responsibilities (resources, risk and reward) are shared (9).

The agency of United States, *Food and Drug Administration* (FDA) was aware of the negative consequences of the drug development situation, so published in 2006 a report with *Clinical Path Opportunities* divided in six areas with 76 specific opportunities that would help enrich the drug development. The six priority topics are (10):

- Better Evaluation Tools: for instance biomarkers;
- Streamlining Clinical Trials: adaptive trial design;
- Harnessing Bioinformatics: develop technological tools;
- Moving Manufacturing into the 21st Century: research oriented to vaccines and biological products;
- Developing Products to Address Urgent Public Health Needs;
- Specific at risk populations – paediatrics.

In Europe, was created the so-called *Innovative Medicines Initiative* that is a collaboration agreement between public and private sector with academia, regulators, biopharmaceutical and healthcare companies. The goal of this collaborations is enhance Europe's competitiveness by supporting the faster development of better medicines (11). *Innovative Medicines Initiative* identifies the following four key hurdles in drug development: difficulty in predicting safety, difficulty in predicting efficacy, a poor knowledge management and gaps in education; consequently, the organization created recommendations related to this "Four-Pillars" (11).

Phase I clinical trials

A key step in drug development is the transition of a molecule from the laboratory to the human subject in a clinical trial. The gateway between scientific research and clinical medicine are Phase I clinical trials.

As stated above, Phase I trials are conducted in a reduced number of healthy volunteers or in patients with a specific disease. Nowadays, the second hypothesis only occurs when it is not ethical to conduct a trial in healthy volunteers due to the severity or specification of drug; for instance, it is not ethical to perform Phase I trials in healthy volunteers with an IMP for cancer treatment (12). Therefore, the main goals of Phase I are to evaluate safety, tolerability, PKs and if possible the pharmacodynamics of the IMP. This phase requires highly qualified experts, because the results of the trial decides the future of the drug. According to Phase I Guidelines of the *Association of the*

British Pharmaceutical Industry, only 60% of the drugs tested in Phase I move on to Phase II, and then only 11% reaches the market (13).

Considering this negative scenario in 2003, FDA declared the urgent need of change and it was introduced a new phase called "Phase 0 (zero)" that lies between non-clinical trials and Phase I. Phase 0 trials are conduct in a reduced number of subjects (healthy or patients), with low doses administrations (also referred as micro-doses) of novel compound, with a low toxicity risk, which allows an early evaluation of PK and pharmacodynamics IMP profiles.
Phase 0 trials reduces the number of non-clinical trials (in vitro and in vivo) required, and also eliminates candidate compounds before they reach Phase I. In this way, Phase 0 improves the efficiency of drug development by reducing costs and time (14).

Generic Drugs and Bioequivalence and Bioavailability studies

As referred, pharmaceutical development is a long and an extremely expensive process, which can be discouraging to a company. With the aim of stimulating the drug development, the medicines authorities extended the duration time of patent protection promoting market exclusivity. Patent protection lasts 20 years after date of registering the drug in the trademark office, and it can be done during any phase of drug development (15). Exclusivity is exclusive marketing rights upon approval of a drug (15). The biggest differences between both concepts are that patent assures the confidentially of drug data (it can end before the marketing approval), and during the exclusivity period, the access to drug data is free, however generics drug cannot be commercialized during this period (15).

In accordance with Directive 2001/83/EC a generic medicinal product "*shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies*" (16).

Two drugs with the same active substance are considered bioequivalent if they are pharmaceutical alternatives and their rate and extent (BA) after administration in the same conditions, lies within the defined limits. In BE studies, to assess the extent of BA, are calculated indicators as the AUC (area under curve from time 0 until the last quantifiable concentration) and C_{max} (peak exposure – maximum plasma concentration). Also to assess the rate of availability are calculated C_{max} and t_{max} (time correspondent to C_{max}). Nowadays, two formulations are generic if the AUC and C_{max}

comparison lies between 80 to 125% (17). The results of BE analysis should generate charts similar to Figure 3.

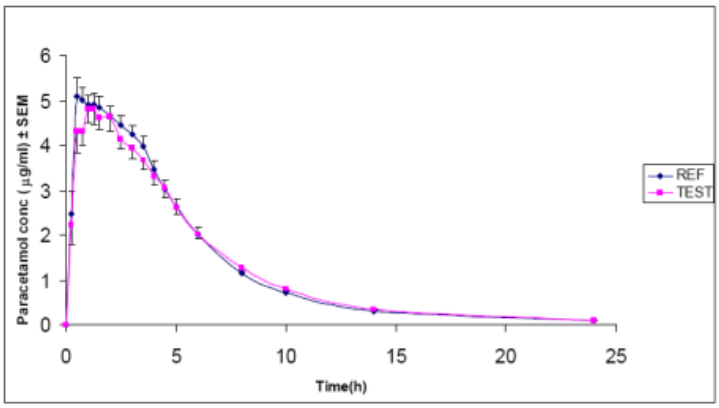

Figure 3 - Example of Bioequivalence chart results(18)

The BA/BE studies design are usually similar to each other, however sponsors must adapt the design in accordance with the specific guidelines to each product. The commonly used trials are (19,20):

- Single-dose: in each period, the volunteer only takes one dose;
- Two-periods: separated by a washout period sufficient to ensure drug elimination;
- Two-sequences: in the first period some volunteers are taking the reference product and the others are taking the investigational product; in second period the volunteers receives the other treatment;
- Randomised: the sequence treatment is random;
- Crossover: all volunteers take the two formulations;
- Open-label: each volunteer knows what he/she will take in two periods, one reference and one investigational product. However, the volunteers must not be informed about each product is being provided.

There are other characteristics that the sponsor have to consider, such as the dietary conditions (subjects dosed after an overnight fasting or after a hypercaloric meal) and if it is a pilot (with a reduced number of participants) or pivotal (with sufficient participants) study (19,20). The inclusion and exclusion criteria of subjects and the blood sampling, must be defined according to the information available about the Reference product.

Regarding the trial design, BA/BE studies are considered “easier” trials, however they are the most complex trials because there is no space to failures or clinical trial protocol (CTP) deviations. To submit a generic drug, *European Medicines Agency* (EMA) only requires a positive study, and

FDA requires at least two trials (fasting and fed conditions) (19,21). Therefore, any CTP deviation is crucial and can throw away the credibility of trial results.

Generic development is a faster process of drug development, since the sponsor has access to the data of the Reference product, and could be only required a clinical trial to prove the BE between the products (19). In this way, the "generic market" is an interesting market once the price can be 30-60% lower than the Reference product (22). It is important that the development of generic drugs respects the regulations in force and must have the same quality requirements that a Reference product (19).

Regulatory Framework

Pharmaceutical industry is one of the highly regulated industries in the world (5). The regulations cover the entire process of drug development since the laboratory research, manufacturing, clinical trials conduction, commercialization and the activities related to detection, assessment and prevention, adverse events after marketing authorisation (pharmacovigilance) (23,24). The main purposes of regulations are to protect the rights, safety and well-being of human subjects (patients or healthy volunteers) and to ensure the quality of data produced (25).
Regarding the clinical trials implementation and conduction, must be taken into account international legislation and guidelines, in combination with national regulations specific to each country. To implement a clinical trial in the European Union, it is mandatory to be in accordance with the following documents:

- Helsinki Declaration. This Declaration is addressed to physicians and contains the ethical principles for medical research in human subjects (26);
- Good Clinical Practices (GCP) of *International Conference Harmonization*: This guideline is an ethical and scientific standard for design, conduction, record and report clinical trials, which assures the protection of rights of trial subjects and the credibility of the data generated (25);
- Directive 2005/28/EC, 8th of April: This directive establishes and details GCP guidelines for IMP, as well the requirements for authorisation of manufacturing or importation for IMP (27);
- Directive 2003/94/EC, 8th October: This directive establishes the principles and guidelines for Good Manufacturing Practice of medicines and IMPs (28);
- Directive 2001/20/EC, 4th April 2001. This directive provides common information related to implementation of GCP in clinical trials for medicinal products for human use (29);

- Directive 95/46/EC, 24th October: The main objective of this directive is to protect the subject confidentially regarding the processing of personal data and on the free movement of such data (30);

In Portugal, additionally to international regulation the national regulation are also applied:

- Law no. 21/2014, of 16th April. This law approves the clinical research, including medicines for human use and medical devices (31);
- Decree-Law no. 20/2013, of 14th February. This document intends to reformulate the National System of Pharmacovigilance to ensure a better detection, monitoring and supervision of the risks related to the use of medicines (32);
- Decree-Law no. 102/2007, of 2nd April. This Decree-Law is a transposition of Directive 2005/28/EC and it establishes the guidelines of GCP related IMP for human use (33);
- Deliberation no. 333 of 2007. This Deliberation establishes a guidance about personal data processing of the clinical trials participants (34);
- *Portaria* no. 396 of 2005, of 7th April. This document defines fees of INFARMED for submission or amendments request of clinical trials (35);
- Decree-Law no. 176/2006, of 30th August. Usually called the Medicinal Product Statute, this document lays down the legal framework for marketing authorisation and other related issues (36);
- Law no. 46/2004, of 19th of August. This Law is transposed from Directive 2001/20/EC, and it establishes the legal framework for the conduction of clinical trials (37);
- Law no. 67/98, of 26th of October. It is a transposition of Directive 95/46/CE of 24th of October concerning the protection of personal data (38).

Clinical Trials in Portugal

As shown, regulatory environment in Portugal is constituted by national regulations and transpositions of European Directives. These regulations together lead to a slow and complex submission process, that is seen as a negative point by foreign sponsors (39). According to INFARMED reports, in the last year, were submitted to INFARMED 114 Clinical Trial Applications (Figure 4), which is slightly lower than in 2012 (118 submissions), but higher than 2011 (88 submissions). In 2013, only a residual percentage correspond to the early phases, and the majority (75%) corresponds to Phase III (Figure 4) (40).

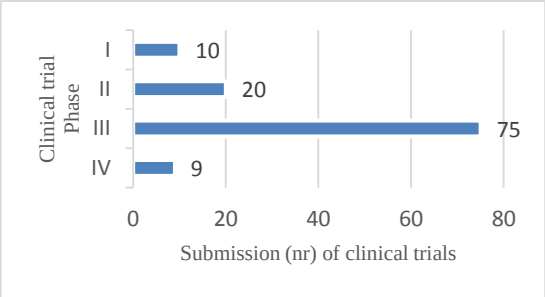

Figure 4 - Clinical trial submissions (nr) to INFARMED in 2013 per clinical trials phase(40)

Considering that Portugal has competent professionals and an excellent scientific capacity in research and health institutions, the results of statistical analysis show a big improvement opportunity to Portugal (39). Comparing with other countries, Portugal has administrative procedures too bureaucratic, that are managed easily in other countries (without compromising the safety of subjects). In this way, the ability to attract foreign investment to clinical research is reduced in Portugal (39).

1.3. TRAINING OBJECTIVES

I had the opportunity to engage in a Portuguese company for this training. Prior to internship initiation, I defined a set of general objectives that are key competences to a professional in pharmaceutical development:

- To improve organizational skills, such as multi-task and time management;
- To improve communication skills;
- To practice problem solving in professional context;
- To develop proactivity performance and leadership spirit including influencing skills.

After my internship started, and taking into account the characteristics of Blueclinical, I set a number of objectives to my internship has follows.

Primary objectives:

- To understand the activities behind a Phase I Unit;
- To act as Project Manager in Phase I clinical trials.

Secondary objectives:

- To perform regulatory submission to the three national competent authorities (CA) (INFARMED, CEIC and CNPD);
- To gain autonomy and became a liaison with regulatory authorities;
- To understand the organization of a Quality Management System;
- To practice medical writing skills;
- To learn other competences related with clinical trials activities.

2. ON-THE-JOB TRAINING

The training was mainly related with Phase I clinical trial in healthy volunteers – BA/BE studies. I also had the chance to collaborate in other external projects to Blueclinical Phase I and to perform tasks not related to the Phase I trials conduction.
In this way, this chapter is divided in two major sections:

- Specific experience which details my experience in Phase I clinical trials in healthy volunteers, mostly BA/BE studies;
- Generic experience which covers five independent themes, that enhanced me the opportunity to develop my competences and were not related to Phase I clinical trials.

2.1. SPECIFIC EXPERIENCE – PHASE I CLINICAL TRIALS RELATED ACTIVITIES

During my internship at Blueclinical Phase I, the main activity performed was acting as CTA. The main functions of CTA are to give administrative support and make sure the implementation of clinical trials in compliance with Blueclinical SOPs, GCP and the applicable legislation and regulation (41). Consequently, CTA have several responsibilities and functions during the whole clinical trial process – before, during and after trial conclusion. In the beginning of my internship, I performed basic tasks, and over time with increasing gains of knowledge and experience, I started executing other tasks which demanded more responsibilities.
This section details my experience and the tasks assigned to me during the internship, and it is divided according to specific procedures, that covers the clinical trial course in sequential order.

2.1.1. STUDY PHASE I REFERENCE DOCUMENTS

One of the first tasks assigned to me, was to study and summarise the *Industry Standard Research* 2013 Report (42) and the guidelines of the *Association of the British Pharmaceutical Industry* (13). The *Industry Standard Research* report is based on a quantitative online survey, which was answered by 119 respondents. The report includes an analysis of the dynamics of Phase I market: the current and expected study volume and some expected changes in the trial, such as, use of patient populations, study complexity and use of multiple sites. This report also identifies the whole process behind outsourcing, as well the sponsors's preferences for several different service provider (42).

The other document, (13), is composed by specific advices that Phase I companies and sponsors must take into account. This document is divided in several sections such as protocol, risk management, competent authorities, subjects (advertisement, screening and payment), pharmacy and IMP, equipment, training, insurance and pharmacovigilance. Those documents are extremely important, because they have information about the trends of the current year and expectations for the future. They also present guidelines that Blueclinical Phase I should consider.
The main reason of this task was to summarise all the information, and then share it with all the team members. This activity was crucial to me, because at the master course focus in Phase I was little, and I felt that I needed to study more about it. At the end of the documents synopsis, I felt more comfortable with the activities related to the conduction of Phase I clinical trials.

2.1.2.INFARMED SUBMISSION

Regarding the GCPs, the conduction of a clinical trial has to be previously authorized by the Competent Authorities. According to the Portuguese Law, number 46 of 2004, 19th August, INFARMED is responsible for evaluating the ratio of risk benefit of the clinical trial and to authorize its conduction (37). Additionally, there is a *Portaria* no. 396 of 2005, 7th April which defines fees associate with the process – clinical trial submission or amendments request (35).
In the INFARMED site, the requester can find supporting documents to the clinical trial first submission and substantial amendments request submission. There you can find a list of documents, required to clinical trial submission, that are considered essential documents:

- Clinical Trial Protocol;
- Informed Consent Form (ICF);
- Investigator's Brochure (if applicable);
- Contract between sponsor and institution;
- Contract between institution and investigators;
- Insurance certificate;
- CTA form and XML file;
- EudraCT number confirmatory document;
- Letter of Authorisation from Sponsor.

In addition, it is necessary a cover letter of the sponsor, asking INFARMED for authorization and the proof of fee payment. All documentation submitted has to be identified with a EudraCT number, which is a unique number that identifies the protocol for a trial regardless of where it will be conducted. EudraCT request is performed online and the clinical trial submission is made through two different forms: paper and electronic form. All documents must be recorded in an

electronic device (CD-ROM) inside the respective folder, previously defined by INFARMED. The structure of the folders is also available at INFARMED site, and it is possible to download it. Besides the documents in electronic format, it is also necessary to send documents in paper form such as cover letter and the clinical trial applicant form, signed and dated.

After INFARMED receives the submission, there is a validation process that is completed when INFARMED confirms that all documents were submitted. After sending the documentation, INFARMED confirms to the requestor that the process is validated and that it will be evaluated. After validation, INFARMED has a legal maximum time to answer the request – ninety (90) days. If the CA asks for additional data, the clock stops until the requestor answers to all INFARMED questions. At the end of evaluation process, INFARMED gives the final decision regarding the trial conduction.

Although INFARMED has 90 days to evaluate the study, the process is usually faster. Accordingly, INFARMED made a public commitment to evaluate BA/BE studies up to half of the legal time (30 days). In fact, INFARMED is making an effort to takes only up to 20 days to evaluate BA/BE studies (43). Taking into account my experience of 8 submissions to CA, I can say that INFARMED usually takes 25 days to approve a BA/BE study.

Even after the INFARMED approval, the trial documentation can suffer changes. If the amendment is substantial – if the change is related to IMP, CTP or it could affect the safety of the participant, an amendment request has to be done. If the amendment is not significant and does not affect the safety of the participant, such as a change of administrative information, a simple notification is sufficient. If some urgent safety measures have to be applied to guarantee the safety of the participant, it can be done without previously authorization. However, INFARMED must be notified during seven days after it (37).

After the end of the trial, the sponsor has 90 days to notify INFARMED about the trial conclusion. This notification consists of cover letter and a specific form, a Declaration of trial completion. The final reports to be sent to CA at most one year after the trial's conclusion.

During my internship I was responsible for the clinical trial submission. My first tasks were to request the EudraCT number from the EudraCT database. Then, I created a table of contents with the required documents and then I identified the person responsible for each one of them. After this, I spoke with the respective person and I informed about the due date to receive the documents. I also contacted the sponsor in order to obtain the "Letter of authorization" signed, and the Insurance Company to obtain the insurance certificate.

Besides the collection of external documents, I was also responsible for creating some documents. Usually I created the XML file and I made the "administrative" supporting documents that are similar to all submissions, such as a list of competent authorities and the list of active trials with the same active substance. Additionally I also wrote the ICF and I did the Quality Control (QC) of CTP.

After archiving all the information the following steps were to confirm if all documents were well placed, confirm if something was missing, and then recorded the folder in a CD-ROM. The last step was performing QC to assure that all documents were saved in a CD-ROM.

Considering the distance between Blueclinical and INFARMED, dossier submission is sent by CTT and the printed documents and CD-ROM are sent attached to the cover letter.

Besides submission, I was also responsible for archiving all correspondence from INFARMED in a shared folder and at Trial Master File (TMF).

The collection of the "external" documents until due date, the signatures of CTP and the contract was very difficult because there is always space to improve the documents, were the biggest difficulties I felt. At the first submission I also had some doubts when I was filling XML file, because it is a new document to me. Other difficult was when I collected all the information from the Sponsor, when INFARMED asked additionally data from IMP. We have a limit data, a maximum time to answer, and sometimes it is difficult to comply because Sponsor takes a long time to answer us.

On the other hand, I did not feel difficulties in acting as liaise with INFARMED.

2.1.3.CEIC SUBMISSION

According to the Portuguese Law number 46 of 2004, 19th August, besides the approval of competent authority, an ethical approval it is also required. In Portugal, the ethics commission is CEIC – Ethics Commission for Clinical Research (37).

Similarly to INFARMED submission, the requestor has to prepare a list of documents and submit it to CEIC as a "paper form" and/or electronic form. The folders structure and the list of documents required by CEIC is not the same as the INFARMED list. CEIC asks less information about the Investigational Medicinal Product, but it inquires about other documents such as:

- Ethics evaluation by Clinical director or Principal Investigator (PI);
- Statement of PI about the site conditions (facilities, collaborators and equipment);
- Case Report Forms (CRF) template;
- Medication circuit and pharmacist declarations;
- Other documents related to heath and quality of life of patients.

The procedures of submission and validation are similar to INFARMED's procedures. After submission, CEIC confirms if all documents were submitted, and then validates the process. After CEIC validation, the process is evaluated by an expertise that can raise questions about additional data or asks to correct some documents. After the requestor responds to all questions, the process is moved to a "plenary meeting". CEIC has plenaries meetings monthly, where the processes are presented, and all participants have to give their opinion (favourable or not). At the end of the plenary meeting, the final decision is available at the site, and a letter and/or a fax is sent to the requestor. Just like INFARMED, CEIC establishes 90 days to give their final opinion about the trial, but the clock can also stop if questions are raised. During my internship CEIC took 38 days (average) to approve the conduction of clinical trial.
After CEIC approval, the requestor can also make changes in the trial documentation and procedures. The process to ask authorization for substantial amendments and to notify a non-substantial amendment is the same as the INFARMED procedure.

During my internship, I was also responsible for CEIC submissions. In order to improve my time management, I prepared both submission dossiers (INFARMED and CEIC) at the same time. However, the folder's structure is different so I had to be careful to save documents in the right folder. After assembling all documents, I verified the dossier to guarantee there were no documents missing. Available at CEIC site we have a "verification checklist" that specifies all documents and details, that the requestor has to accomplish. Usually I used this checklist before the dossier submission.
The difficulties I felt with the CEIC submission, were similar to the INFARMED submission. Another difficulty that I felt was tracking correspondence received, because CEIC does not have a standard communication procedure. Sometimes CEIC sent a fax and a letter, but in other occasions, CEIC only sends a letter. A disadvantage of this situation is the delay of two/three days of letter receipt when comparing to the fax, so the sponsor or monitor, can think the documents are missing

2.1.4.CNPD NOTIFICATION

The CNPD (*Comissão Nacional de Proteção de Dados* - Portuguese Commission of Data Protection) is a national Commission that supervise and monitors the processing of personal data, in a strict right respect for human rights. According the Portuguese Law 67/98 of 26 October, CNPD is responsible for authorizing the processing of personal data. Among other functions, CNPD must also ensure the right of access to data (38).

There is a Deliberation related to data protection at Clinical Trials, based on the Law stated above. The aim of the Deliberation number 333 of 2007 is to establish a guidance about processing of the personal data of the participants clinical trials (34).

Considering those regulation, before the Clinical Trial initiation, the authorization of CNPD is also required. The Notification to CNPD is made online via www.cnpd.pt. The online form just ask for information about data collection and processing. The most important questions are the type of data collected, other entities/countries who have access to the data and what safety measures will be taken. After the submission it will appear a message that contains an identification number of the notification and the instructions to for the payment by the requestor.

CNPD notification involves a fee payment, that is a fixed fee to all type of notifications, and corresponds to 150€ (44). The payment proof must be sent by email to cnpd.pagamentos@cnpd.pt. If the payment is not done within three days after the notification, the process is rejected.

Then, CNPD sends an email with the receipt of payment where they identify the process with an internal number (number/year). From this moment on, the identification number must be used in all communications with CNPD.

CNPD questions about a specific process (if applicable) and the final authorization are always received by email. CNPD never sends a letter or a fax, its communications are always by email.

During my internship I submitted some notifications to CNPD. Before the online submission, I fulfilled a template in the CNPD site (in Word format) with all the required information. Then, CRM reviewed it to validate all information, I copied it to the site and I did the online submission. After this, I sent an email to geral@cnpd.pt with some documents attached, that were complementary to the online submission (usually I sent ICF, synopsis of CTP, eCRF (electronic Case Report Form) model, justification for the race/ethnicity data collection and the list of entities which have access to the data). Then, I sent an email to the financial department of Blueclinical asking for the fee payment. When the proof of payment was sent to me, I forward it to CNPD. From this moment on, I only had to wait for the authorization or some questions.

CNPD does not have a maximum time to give their opinion about the submission. From my experience I can affirm that CNPD took 42 days (at average) to authorize the data collection, however the procedure duration became faster in the recent submissions. During my internship, if no questions were made by CNPD the process could last between 13 to 26 days; additionally if the committee asked questions about the process, it could be extended up to 59 days. So, it can be a slow process and it can delay the trial initiation.

In order to obtain a quick authorization, I had two strategies. One of them was to explain that the data collected in the trial, was the same of previous submissions (and I identified the CNPD internal number). The other strategy was often calling to CNPD to know the status of the

evaluation process. CNPD authorized all the submissions I made, some of them without asking additional data and Blueclinical never delayed a trial initiation because of the CNPD authorization.

2.1.5.INVESTIGATORS MEETING

Before the trial initiation, the staff members – clinical and non-clinical – had to be trained at least in GCP, Blueclinical SOPs and in the CTP. To guarantee that all collaborators have the appropriate training, before the initiation of the trial, an Investigator's Meeting is scheduled. All members have to attend the meeting and sign the "Meeting attendance" sheet. The presence in this meeting is mandatory; who do not attend the meeting (and who do not sign the sheet), cannot participate in the trial.

The themes discussed in the meeting depend on the team experience. If the staff is new in the field, the meeting must contains GCP and SOPs training. If the staff is already trained, the meeting must give more importance to the Protocol.

At the Meeting, the PI presents in detail the CTP: the IMP, study objectives, study design, selection criteria (inclusion and exclusion), clinical trial procedures, the blood sampling, and the safety assessment, screening and enrolment procedure including randomization, reporting procedure of Suspected Unexpected Serious Adverse Reactions and Serious Adverse Events and subject discontinuation.

Thus, other team member introduces the Source Documents (SD) and the eCRFs. The Source Documents are the papers where the data is registered in first place. The CRF is printed or electronic (eCRF) documents may be used to collect and record CTP required information (45). Additionally the team's improvement opportunities can be discussed.

At the end of the meeting, the staff has also to sign the "Delegation of tasks". In this document, PI authorizes investigators and non-clinical staff to participate in the trial, and also defines functions and responsibilities of each collaborator.

During my internship I attended some meetings, and I also prepared them. The first steps was calling all investigators and confirm their participation in the meeting. Then I prepared all the supporting documentation: the meeting dossier (to give to each investigator), the Delegation of tasks and the Meeting Attendance. I usually was also responsible to collect all the signatures in the end of the meeting. In addition to this, in some meetings, I presented the Source Documents, because I was familiarized with them, taking into consideration other activities performed during the internship.

2.1.6. VOLUNTEERS RECRUITMENT

After the authorities' approval and the investigators meeting, the following step was recruiting healthy volunteers. Blueclinical Phase I has an online database (approved by CNPD) where the candidates have to register themselves. At the online platform, the candidates fill in the name, email, phone contact, and some personal information such as age, weight and height.
The recruitment is made through phone calls to registered candidates. Before the recruitment, a "*Memorandum of recruitment*" has to be created. This supporting document is based on information presented in the Protocol and in the Informed Consent, and it must comprise all information about the trial that should be explained to the volunteer.
During my internship I built some *Memorandums* that were reviewed by CRM. The *Memorandum* is also reviewed by PI, and it can only be used after the approval and signature of CRM and PI.
The following step is to phone to the volunteers. Before I made my first call, I attend to an internal training session, presented by CRM, where it was explained how to proceed during the phone calls. The first thing to do is to confirm the name of the candidate, and confirm that he had registered himself at the online platform. After this confirmation, and if the candidate still wants to participate, all information about the trial is presented. Another important conclusion is that there is not a standard phone call, because it depends on the questions of the candidate. At the first day of recruitment, I attended to some phone calls made by CRM in order to hear and understand several real situations. At this training section I also learned that it is mandatory to recruit substitute's volunteers. When I heard this information for the first time, I thought that was not fare recruiting extra volunteers. However, I quickly I realized that they were essential, because the volunteers may not be as healthy as they though, and some of them can give up and do not show at screening or admission.
After this training, I started making phone calls near to CRM: because I could need some help during the call, and she would also evaluate if I was doing a good work.
Over the gained experience, I confirmed that the *Memorandum* was helpful, however, there is not a standard call. With the experience I also had the opportunity to define the better method to recruit more efficiently.
I usually started with the dates of the trial, because it is a crucial exclusion criteria. If the candidate does not have agenda in the dates presented, the phone call ends rapidly. If not, I present the study information such as the objective, design, blood sampling informing about some restrictions that they have to comply with, alongside with some details about the medicine that will be tested. For ethical reasons, the last topic of the *Memorandum* that I inform, is the value of financial compensation, unless if the candidate asks me before.

If the volunteer has no doubts and still wants to participate, the following step is asking some questions about the main inclusion/exclusion criteria. If the volunteer complies with the selection criteria, a screening visit is scheduled. Depending on the CTP, the volunteer has to respect some restrictions (dietary and/or behavioral) before the screening, because of the safety analysis performed at screening and the possible interference with the experimental medicine. The phone calls ends with the confirmation of the date and hour of the screening.
One or two days before the screening visit, I telephone the candidate again with the aim of remembering the hour of the visit and the restrictions that they have to comply with. Additionally, this phone call works as an extra motivation to the volunteer (when the volunteer is thinking about giving up).
During my internship I enrolled this function at all trials. This was not a hard task, because I had the *Memorandum* to guide me. I appreciated calling to candidates explaining the trial and clarifying their doubts. The first calls of each trial were very exciting. However, after a few calls I started feeling tired, because I had to repeat the same text many times; it was also demotivating when candidates did not have time to participate or when volunteers did not want it. So, although this work was not one of my favourite tasks, after my trainee I can say that I was capable to recruit volunteers.

2.1.7.SCREENING

Before the candidate can enter in the clinical trial, he must go through a screening process. The main goal of screening is to assure the healthy condition of the candidate and help the investigator determine if the candidate is eligible to participate.
Screening has a medical appointment where the medical history is collected, a physical examination is performed (including vital signs); it is also performed an electrocardiography, blood and urine are collected to safety analysis (haematology, biochemistry, viral serology, coagulation, urine analysis, drugs, and pregnancy if woman). The data collected is all recorded at an appropriated Source Document (each volunteer has one).
Screening can only be initiated after the volunteer signed the ICF. At Phase I clinical trials, the signature of ICF and the screening visit occurs at the same day. This is only possible because before the screening visit, the volunteer receives all the information needed about the trial and he is already motivated to participate. However, the volunteer has always to read the ICF (at least 30 minutes are provided for the volunteer to read the ICF). Then the volunteer will talk with the RP, who explains the clinical trial and clarifies all doubts to the volunteer. Only after this explication, and if the volunteer is willing-to participate, two copies of Informed Consent have to be signed by

the volunteer and by the RP. Then, a medical appointment happens and the volunteer leaves Blueclinical.
Some hours after the end of the screening, the principal investigator receives the laboratory results of the safety analysis, and PI or a RP authorised has to analyse the whole SD and review the inclusion/exclusion criteria. If the volunteer complies with all the selection criteria, the volunteer is eligible and can participate in the trial. If the volunteer has just only one-exclusion criteria or do not complies with the inclusion criteria, he is not eligible and, therefore cannot participate.
During the screening period, I have an active role related to the volunteers. After the volunteer arrives to the Blueclinical, I confirmed his identity with the Identity Document, and I asked him to sign the Visitor Log Book (everyone external to Phase I has to sign it). The next step was to provide a comfortable ambient to the volunteer at the "waiting room" with me giving him the Informed Consent to read during at least, 30 minutes. After this, I coordinated the order of volunteers for medical appointment, specimen collection and electrocardiogram.
At the end of the visit, I gave one ICF to the volunteer and I archived the other one on the TMF. As CTA, I can also explain the non-clinical doubts, such as the time of admission and what kind of personal belongings can the volunteer bring to the Blueclinical. The visit ends with the signature of the Visitor Log Book.

2.1.8.ADMISSION

As previously done at screening, before the admission, a phone call to the volunteers must be made. The main goal is to confirm that the volunteer still wants to participate and the hour and the restrictions required are also recalled.
The admission occurs in the afternoon in the day before the "dosing day". According to CTP, the medical history and the physical examination have to be updated, and some laboratory tests have to be repeated (usually drugs abuse in urine and pregnancy).
At the first admission, after the laboratory results are available, PI or RP designee analyses if the volunteer can be included on the study or not. After PI authorization, the included volunteers are randomised and the volunteers that were not included (substitute and/or not eligible volunteers) leave the Blueclinical facilities.
After the randomisation, the volunteers are identified with the randomisation number and the confinement phase starts. Included volunteers have to wear the Blueclinical uniforms, and lock their personal stuff into the lockers. The dietary restrictions starts and a standard dinner is served to all.

Each trial has usually two admissions. The only difference between them is the presence of substitute volunteers on the first one. Only the included volunteers in the trial will return to the second confinement. As performed in the first admission, the medical appointment and the laboratory tests are repeated. After the laboratory results are available, PI has to authorize the volunteer participation. At this time, there is no randomization – volunteers keep the same randomization number during the whole trial.

As CTA in this phase I received the volunteers at Blueclinical, and asked them to sign the Visitors Log Book. I also managed the doctors and nurse appointments, often I went to deliver the urine collections to the laboratory, and waited for the results (received by email). At the first admission I also delivered the Blueclinical Phase I rules that volunteers had to read and sign.

After the PI authorization of subject enrolment, I worked with the RN identifying the volunteers with a bracelet and giving them the uniforms to wear. I also helped the RN serving the dinner and registering the start and end time of meal. Each volunteer receives a "work plan" which details the time, procedure performing it during the confinement. This way the volunteer previously knows when has to be able for the procedures.

2.1.9.CONFINEMENT PHASE

This phase starts with the admission of volunteers. During the confinement phase, volunteers have to respect the rules of Blueclinical as well as the CTP specifications. All the meals are provided by Blueclinical, and they cannot eat food that they bring from home. They also have to respect the restriction of water intake (the period of time depends on CTP).

Depending on the study design, volunteers have to take the medicine after an over-night fasting or after intake of a hyper caloric meal. The time of blood collection is defined by the CTP, but usually the collections are closer in the first hours after dosing.

The tasks assigned to each Blueclinical collaborator are previous stabilised, and each one knows what have to do. The RP have to administer the dose, measure vital signs, and register the adverse events (if it happens). The RNs have to collect the blood samples ate the scheduled time and measure the volunteers' vital signs. Research pharmacist has to dispense the dose, and can be witness of the dose administration. Laboratory technician has to centrifuge the blood samples, and pipette and storage the plasma.

As CTA I was responsible for serving the breakfast, lunch, snack and dinner (if applicable), registering the start and end time, and I also had to write down some comments if the volunteer did not eat the full meal. The meals were served individually, with a difference of 5 minutes between volunteers. The BA/BE studies are very strict, with a controlled one minute time of meals, for

instance, if the breakfast starts one minute after the scheduled time, the time of drug administration has to be delayed a minute of the planned hour.
Additionally, I monitor the Source Documents on-going to guarantee that they are correctly filled. I also tried to be available to help RN and RP if necessary. When I had free time during the trial, I verified the content of TMF and I archived the documentation that was missing.

2.1.10. END OF STUDY OR FOLLOW UP

Depending on the study design, the trial can end in the last day of confinement or can end at a later visit named "Follow up." The aim of these procedures is to guarantee that the "healthy condition" of each volunteer, was maintained.
If the CTP requires a Follow-up visit, the volunteer has to return to Blueclinical, some days after the end of confinement day. At this visit, the medical history and the physical examination are updated. It is also collected blood for safety analysis (haematology and biochemistry).
If the CTP defines that the trial ends at the last confinement day, at the last PK blood collection, the RN also collects blood for a haematological and biochemistry tube. The discharge of volunteer is only authorised by a RP, after a medical appointment with the volunteer. At the end of the first period, I only had to assure that the volunteer signed the Visitors Log Book and to remember the date of the next confinement.

At the end of the last confinement phase or at the follow up, I had to give specific information about the financial compensation. For accounting purposes, volunteers have to emit an Invoice named "Ato Isolado" or a "Recibo Verde" to justify the money received by Blueclinical. Some volunteers are not familiar with this financial procedures, so we had to explain it to them. Additionally we gave a document with the steps to emit online an invoice and with information to fill the gaps. I had also to collect personal information such as address, VAT number and bank identification number, to complete the supporting document about compensation request. This supporting document is sent by email to the financial department to inform them about the bank transfer. Then, I waited for receiving by email the volunteer invoice, and then I asked for the bank transference.
The duty of being responsible for volunteer's compensation helped me to improve knowledge in Portuguese financial system, because before the first trial, I had to study and to understand how it worked. It was a challenge leaving out of my comfort zone.

2.1.11. BLOOD SAMPLES PROCESSING AND SHIPPING

In Phase I trials there are two types of blood collection. One of them is for the safety analysis (detailed above) and the other is for PK analysis.

The blood tubes collected for safety analysis were delivered at the Laboratory of Prelada Hospital minutes after the collection. Sometimes during the screening period, the haematology tubes are centrifuged in Blueclinical, because they have to be centrifuged between thirty and sixty minutes after collection. The tubes and the labels are provided by HPLab. To assure the data protection of the volunteer, Blueclinical never provides the volunteer identification to HPLab – Blueclinical only provides the internal number (screening number), sex and the date of birth.

The PK analysis is performed by international laboratories that are certified to this work; unfortunately in Portugal there is no laboratory certified for PK analysis.

Before the trial initiation, it is necessary to create labels for blood tubes and microtubes. CTP defines what data must be written in the labels, but usually they have to include the Blueclinical name, CTP code, volunteer randomization number, study period and aliquot number, and a statement with the purpose of the blood/plasma. After that, it is mandatory to perform the QC to assure all labels are correct. Furthermore, a copy of the labels has to be archived at TMF. The next step is to label the tubes and microtubes, and organize them at the supports. It is also necessary to identify the freezer storage boxes, because the microtubes are stored at freezers of -20ºC and/or -80ºC.

Another thing to do before the trial initiation, is creating a centrifuge plan. CTP sets the maximum time for samples to centrifuge, which has to be strictly followed. With the plans, the laboratory technician has been informed about the times of centrifugation and also what tubes have to be centrifuged at that time. After the tubes centrifugation, the plasma has to pippeted and transferred to the microtubes. The quantity of plasma is defined at CTP, and usually two aliquots of plasma have to be separated in microtubes. Samples have to be stored at -20ºC and latter can be transferred to -80ºC (if applicable). After the end of the study, a qualified transport company sends the samples to a laboratory, these samples are transported at appropriate boxes, surrounded by dry ice, and with a logger to register the temperature variations.

All the temperature records (freezer logger and the fight logger) have to be archive at TMF. If there are some deviations to the limits defined at CTP, they have to be justified.

During my internship I also had the opportunity to perform some duties at the laboratory, because for a period of time, Blueclinical had a lack of laboratory technicians. In first place, I had a theoretical training given by the laboratory coordinator, and then I had a practical training. I also performed an e-learning course of IATA (International Air Transport Association) to get to know

more about the air transportation of blood samples. I made labels for the blood tubes and performed the QC for the labels of other trials (the person who makes the labels cannot do the QC). Furthermore, I was responsible for centrifuge, pippete and store the samples during certain hours. I worked at night shifts because the collections were more spaced between them, and I had more time to do it. Although the night shift was smoother, it was a big responsibility staying alone at the laboratory. I enjoy performing these duties during my training, however I do not want work as laboratory technician in the future.

2.1.12. SOURCE DOCUMENTS AND eCRF

As stated before, a Source Document is a document in which all data collected during the trial is first recorded. If the investigators wrote in a post-it the vital signs, the post-it is the SD. SD includes clinical findings and observations, or other data that can be used by the investigator.
SD structure must be compliant with CTP requirements, so each trial has to have their own SD.
The electronic Case Report Form is an electronic format SD. One advantage of eCRF is that enables data to be systematically captured, managed, analysed and reported (46).
Nowadays, most companies use paper SD and then a Data Entrée copies the data to eCRF. However, this process takes a long time and is associated to transcription errors.
The best option is to record date directly in an electronic format. This eliminates data duplication, facilitates remote monitoring, removes the transcription errors (SD into eCRF) and facilitates the collection of whole data (46).

During my internship the SD was in paper format, and then a team member acts like Data Entrée and copied the data to eCRFs. The fields required at SD and eCRF were defined by CTP. SD was prepared by team members of Blueclinical Phase I and the eCRFs were designed by Data Manager of the Blueclinical. SD has not to be a translated version of eCRF, the SD can contain more data that is not required by CTP and not found in eCRF.
During my internship I prepared some SD (I made some adjustments and improvements of the last version). Additionally I was responsible for the QC of eCRF, I had to evaluate if eCRF was compliant with CTP and I also had to check the software online.
After the trial initiation I monitored the SD to assure fields were recorded, signed and dated. At the firsts clinical trials it was one of the biggest problems, because investigators were not familiar with the SD and with GCP corrections. It was challenging explaining and convincing investigators to sign and date below each data they recorded. Nevertheless, investigators rapidly started to record data at SD correctly.

2.1.13. TRIAL MASTER FILE

According to regulatory authorities and GCP, all companies involved in clinical trials have to maintain and store all documentation related to trial. Those documents have to be archived at TMF. All documentation proves the trial was (or not) conducted according the CTP, GCP, SOPs and regulatory requirements and it also allows evaluating the quality of the data produced (25). Considering the Guideline of GCP, there are three phases of archiving documents: before the trial initiation (such as CTA, correspondence received from competent authorities), during the trial (such as the signed ICFs) and after termination of the trial (such as completed CRF) (25). Monitors at all monitoring visits review TMF, and it is usually audited and inspected by the authorities or an independent auditor. Despite the TMF is seen as something mandatory by regulators, TMF is extremely helpful for the institution site and to sponsor to manage the clinical trial.

During my internship I was also responsible for creating the TMF dossiers, archiving the documentation and monitoring them. Blueclinical has a specific supporting documents, based on GCP guideline, which details the sections that TMF has to contain.

Creating the TMF structure was very easy, however filling the sections with the right contents was not that easy. I had never seen a TMF, and I had no idea how to complete it. When I was completing my first TMF, I was under supervision all the time, because I had a lot of questions. Nevertheless, I learned it quickly enabling me to do the following TMFs alone. All of them were revised by other collaborators of Blueclinical.

The biggest difficulty I had was completing the laboratory and IMP sections, because I was not comfortable with all the documentation related to these topics. However, the TMF completion is a responsibility of CTA, so if something was missing at TMF I had to ask my colleagues for documentation. With the experience I became more familiarized with the documentation, and this process got easier.

2.1.14. PROJECT MANAGER

A Project Manager is a person who has the responsibility to manage a project, which includes organize, coordinate and close it. There are some responsibilities that are common to all project managers, such as manage all the stakeholders and all the team collaborators, manage the schedule, budget and risk. A project manager is also responsible for ensuring that all team collaborators are motivated.

During my internship I had the opportunity to perform some duties of project manager in Phase I clinical trials, initially under supervision and later with independence to act by myself.
As a project manager, I was responsible for the following items:

- To ensure that documents required were available to the CA submission in the planned date;
- To work as liaison with authorities, and to ensure the additional data was sent faster as possible;
- To work as liaison with sponsor, and to be able to clarify all doubts or concerns. If there were no communications between Blueclinical and sponsor, an email with a weekly report had to be sent;
- To work as liaison with trial monitors to schedule the visit dates and to receive the visit report;
- To ensure the clinical and non-clinical staff was trained in CTP;
- To ensure the Unit was ready for trial initiation: sufficient clinical and nurse supplies were available and Prelada's Hospital services were scheduled (catering, laundry and cleaning);
- To ensure the volunteers recruitment;
- To ensure that all documentation related to the trial was archived in the TMF.

One of the difficulties I felt during this role was communicating with the sponsor, because sometimes I did not know what information could be shared. Additionally, information could be misunderstood by sponsor, and all written correspondence could work as legal proof in the future. I also had the chance of working with a foreign sponsor, so all communications were in English, which increased the challenge. Although communication with sponsor was difficult for me, it was also my favourite task.

2.1.15. AUDITS AND MONITORING VISITS

When my internship started, Blueclinical was a new company. The initial main goals of Blueclinical were building a strong company with excellent professionals and good procedures.
In order to get new partnerships, Blueclinical had the doors open to receive companies and to present Blueclinical facilities. Before the first visit, it was necessary to assure that everything was ready, such as:

- Facilities had to contain all required equipment;
- SOPs had to be finished, approved and signed;
- All documentation was duly signed;

- All collaborators had to know their own functions during the visit – if they had an active role or not.

There are different types of visits. Some companies perform a visit as an Audit, to evaluate the feasibility of a partnership. Those type of visits are extremely complete and it can take more than one day. Those visits include facilities presentation, SOPs consulting and interviews to some collaborators. After the visit, the company usually writes down a visit report. The other type of visits are simpler than audits, because the procedures discussion and the interviews occurs during the Blueclinical facilities presentation.

During my internship I had the great opportunity to participate at a preparation of the first visit as "Audit" of a foreign company and the first inspection by INFARMED. It was challenging to the entire team because Blueclinical had to assure that all items stated above were ready before visit. For me, it was an extra motivation to watch and feel the team spirit to get all ready.

2.1.16. SUPPLIERS AND STOCK MANAGEMENT

When my internship started Blueclinical did not have, until then, all necessary equipment. So, during a couple of times I was responsible for asking for several equipment quotation. The first step was to consult on internet which companies were selling the product. Then, I telephoned them to explain what proper equipment Blueclinical was looking with which specific requirements. I asked for advice when there were several of brands and models. When I received the quotation I did a table on Excel with a maximum of five hypothesis, where I present: the name of supplier, brand and models, product specifications, price with and without VAT and the costs of transportation if applicable. Then, I sent this table to CRM, in order to obtain a final decision. The last two steps consisted of calling to the chosen supplier, to inform that Blueclinical approved the quotation, and then sending an email with the same information. The email worked as a written proof.

When the equipment arrived to Blueclinical, it was necessary a calibration or verification (it depending on the equipment). I was also responsible for hiring the service, scheduling the date. In addition to these large purchases, I also bought clinical, laboratory and stationary material.

During few months I managed the stock. Blueclinical has also a supporting document to manage the stock of clinical, nursing, laboratory and stationary consumables. The document includes the product name, reference, supplier, minimum quantity, actual quantity, the place where it is stored and a free space for comments. This supporting document must be updated weekly to assure the minimum quantities are available and to manage the need of placing a new order.

This duty helped me to improve my communication skills, because I spent a lot of time on the telephone with potential suppliers. During the phone calls I explained what Blueclinical wanted, if I were asked for more information and also tried to negotiate the final price. It was challenging because I am a shy person.

2.2. GENERIC EXPERIENCE

During my internship I had the opportunity to collaborate in the three divisions of Blueclinical and to explore different areas of clinical research. I had the chance to develop experience in medical writing, quality management, Phase I trials in specific population, business development, clinical monitoring and medical devices. All of these activities occurred simultaneously with the main activity – Phase I clinical trials in healthy volunteers.
Considering the diversity of the themes, this section details each theme in a separated topic.

2.2.1.PHASE I CLINICAL TRIALS IN SPECIFIC PATIENT POPULATION

Phase I is a gateway between scientific research and clinical medicine because, for the first time, potential new medicines are administrated to humans. Before human administration, non-clinical studies have to be conducted in vitro and/or in animals to study the PK, pharmacodynamics and toxicity. Phase I trials are usually conducted with healthy subjects, however they can be conducted in patients population. The decision of trial subjects should be made on a case-by-case scenario, however for safety and ethical reasons some IMPs such as cancer therapy and gene therapy should be administrated only to patients with target disease (12,13).
As stated before, Blueclinical Phase I conducts Phase I trials in healthy volunteers (at Pharmacology Unit) and Phase I trials in specific populations (at CUF Hospital).
Although clinical trials in specific populations are conducted at the CUF Hospital, all administrative work is supported by Phase I collaborators. During my internship, I had the great opportunity to help CRM at proving administrative support of the first clinical trial of Blueclinical in specific population.
The medicinal product tested in this trial was a new chemical entity, LUZ11, together with a photodynamic therapy. This method involves the administration of a light sensitive drug (LUZ11) followed by a light of an appropriate wavelength. This treatment is used at palliation of head and neck-advanced cancer and the primary goal of the trial is to assess the tolerability of LUZ11. The secondary goal of this trial is to explore the anti-tumour effect of treatment in therapeutic approach.

During my internship I helped CRM with Competent Authorities submission dossier, and then I acted as liaising between Blueclinical and CAs. I also reviewed CTP, translated the synopsis of CTP and I also wrote a draft version of ICF. Due to a temporary absence for personal reasons of the CRM, I also became the contact person with the sponsor to update about the CA submissions status.

This duty resulted in personal enrichment for me for several reasons. The contents of documents required for CA submissions were different from the ones I used to create, because facilities, collaborators and the details of trial were completely different from the Phase I in healthy volunteer's documents and details. I also worked with external collaborators to Blueclinical Phase I.

2.2.2.CLINICAL TRIAL MONITORING

GCP guideline defines clinical trial monitoring as the act of overseeing the conduct of a trial, to verify if the rights and well-being of human participants are protected. Another purpose of monitoring is to verify if the reported data is accurate and complete, and to ensure that the trial is conducted according to CTP, SOP, regulatory requirements and GCP. Clinical trial monitors should be properly trained to the job and should be familiar with CTP, ICF and other written information, including SOPs and regulations. Choosing a monitor is a responsibility of the Sponsor (25).

Monitoring visits can be divided in four types (47):

- Pre-study visit or Site Qualification Visit: is conducted to evaluate if the site, the principal investigator an clinical team, have capabilities to conduct the trial;
- Site Initiation Visit: is conducted after the site has received all approvals required and before the trial initiation in that site. It is another opportunity to evaluate if the investigator understands her/his responsibilities;
- Period Monitoring Visits: these visits can occur every weeks or once a year, it depends on a plan (or contract) defined by the sponsor. The main goal of these visits is to evaluate the status of the trial as well as the Source Documents;
- Clouse-out visit: This type of visit occurs when the trial has been completed in the site.

The first project of Blueclinical R&D was to give administrative support to a foreign company, who intended to conduct a study of a medical device in Portugal. The mission was accomplished, Portuguese authorities approved the study and it was conducted in several Portuguese hospitals.

After this step, Blueclinical was also responsible to perform monitoring visits to the sites during the study.

The site's investigators had the responsibility to fill in the study documents and archive it in the proper binder. This administrative procedure is the major problem for the sites, because investigators have no free-time and no interest to perform this task. Therefore, the performed medical reports and the written proofs of the study, are not available.
To guarantee the subject rights were protected, the reported data was accurate and completed, and to verify if the study was conducted in compliance with the protocol, regulatory requirements and GCP is necessary to perform the study monitoring visits. A monitor chosen by the sponsor performs these visits. The monitor should be trained, should have clinical knowledge and be familiar with CTP, ICF, regulatory requirements, CGP (25).
Blueclinical was also subcontracted monitors to perform the monitoring visits to this study. The first monitoring visit occurs before the trial initiation in a site, to guarantee the site is capable to conduct the study. Then, each monitoring visit is different because it depends on the study status, i.e. if there are new subjects screened, enrolled or excluded.

I had the opportunity to participate in one monitoring visit to *Centro Hospitalar Entre Douro e Vouga E.P.E.* with a responsible monitor. Considering that new subjects were not enrolled, this visit was a quiet and uncommon visit. During the day, the monitor reviewed the TMF to guarantee that all documents were available and duly signed, and verified if the source documents of each subject's data were correctly recorded and if the study was conducted in compliance with the CTP. In this visit I had the chance to see a different TMF organization, other templates, and essentially I discovered a reality completely different from Phase I clinical trials. In Phase I everything is much controlled and minor mistakes are not accepted, which not happens in the hospitals. In hospitals finding an investigator available to talk about the trial status or to correct some documents is very difficult.

2.2.3.MEDICAL WRITING

Medical writing is a generic definition that includes writing different types of scientific documents such as drug or disease related, research related and articles in journal. In clinical trial context, medical writing includes writing the CTP, ICF, investigator brochure, final report and statistical plan among other documents (48). Medical writer can also review and perform the QC of the documents.

Blueclinical SOPs define the data that must be included in each document. At the end, a QC must be done to assure the document compliance with SOP. This procedure includes document review and a simultaneous filling of a checklist, which has to be signed and dated at the end by the reviewer.

During my internship I had some duties as a medical writer that included writing, review and QC of several documents, such as CTP (in English), ICF (in Portuguese and in English) and financial agreement (in English). I also performed translation of CTP synopsis (from English to Portuguese) and of ICF (from Portuguese to English).
My first experience was to review a CTP to evaluate the coherence of the text and to correct possible minor errors. With training, I started to review ICF and draft versions of contracts between Blueclinical and Sponsors.
After performing some documents reviews, I started writing ICFs in Portuguese. ICF consists of two parts: information sheet and the consent certificate. The first part contains all information about the trial written in a clear way, based in the CTP of the trial and the Summary of the Product Characteristics of the drug. The second part is where the volunteer confirms his/her willingness to participate in the trial, by signed and dated ICF. Before the inclusion of volunteers in the trial, ICF has to be signed and dated by the subject and the investigator (25,49). The participant signature confirms the subject was informed of all trial details and still wants to participate, and the investigator signature confirms this procedure was conducted in compliance with regulations (50). ICFs are written at local language, however if the Sponsor is foreign, ICF has to be translated to English. During the internship I reviewed, wrote, translated and performed QC of several ICFs. Related to medical writing, I also translated the CTP synopsis to Portuguese, because it is a mandatory document of CEIC submission. Taking into account Blueclinical SOPs, all translations had to be followed by a Translation Certificate which includes the title, version, date and documents languages. Translation Certificate has to be signed and dated by the translator and the original certificate must be attached to the document in TMF.
Although this area is not one of my favourites, I did like the experience because the review tasks promoted my critical thinking and the written tasks helped me to improve my written English.

2.2.4.QUALITY ASSURANCE MANAGEMENT

A SOP is a set of written instructions that must be followed to obtain a desired outcome. The SOPs purpose is to ensure the operations are carried out consistently – correctly and always in the same manner (51). SOPs must be written in a clean way, without unnecessary words. In order to

stimulate the SOPs consultancy they cannot be too extensive, however they have to include the necessary information. SOPs can have Supporting Documents attached such as flowcharts, forms, labels and work instructions (52).
The recent companies do not have SOPs, because they have to be written by the collaborators of the company. During the first times of the company, SOPs were considered by many collaborators unnecessary, however with the company's growth, SOPs became essential. After SOPs approval by the responsible persons (this information also has to be defined in the company SOPs), every collaborators related with the SOP context had to read and understand SOP.
SOPs are living documents that can be changed and updated, to improve/clarify/revoke the procedure. The version number and date of SOP has to be updated, and all collaborators have to be informed and have to read the new versions. The proof of training in new SOPs have to be archieved in a proper binder. Nowadays, an email with the following statement "I have read and understood the SOP" can act as proof of SOP training. These procedures leads to a successful quality system.

When my internship started, Blueclinical was writing the first version of their SOPs. There was no SOP to guide and help the team, so collaborators had to ask for help and clarifications when they did not know how to proceed.
In the beginning of my internship I supported CRM by writing SOPs related to Prelada's Hospital services. I attended a meeting with the responsible for the General Services of the Hospital, where we discussed the procedures of the laundry, cleaning, security and canteen. Then, considering the meeting, I wrote a draft version of the SOPs and supporting documents. Before SOPs entered into force, the draft version was revised and approved by CRM, Managing Partner and the Quality Assurance Manager.
After a few months of consulting and working according to the SOPs, Blueclinical concluded some SOPs had to be improved. All collaborators were invited to review and give their own feedback. I suggested a review of the SOP of clinical trial submission to Competent Authorities, and then I submitted the suggestions in a document with tracked changes. My review suggestion gave the procedure a little more detail very succinctly, to assure that there were no doubts. I also created some supporting documents to guarantee the quality of the documents submitted to the authorities. The SOP revision was very interesting to me, because I had to review the mental procedure to certify that there was no loss of information.
I am very glad to have experienced this activity, because it made me realized about the impact of a SOP and the negative impact of a poorly written or ambiguous SOP in a company. Writing and review SOPs also helped me to develop my communications skills.

2.2.5.BUSINESS DEVELOPMENT

When my internship started, the network of Blueclinical CRP was in expansion. At that moment Blueclinical was introducing itself, mission and goals, to administration boards of the Portuguese hospitals. If the Hospital agreed with the partnership with Blueclinical in clinical research, a financial agreement was signed for both parts.

One of my first tasks in business development was to research the name of each Chairman of the Hospital Administration Board and its email and phone contact. Then, an email to the Chairman was sent, in order to introduce Blueclinical CRP mission and goals and to propose a meeting between Chairman and Blueclinical.

After this email, I was responsible for contacting Hospitals to get an update. Those phone calls had three main goals, first, know if they already saw the email; second, show that Blueclinical was interested in the partnership and, finally, to put a little more pressure on Hospital decision. During this procedure, I had to fill the "*memorandum of conversations*". The memorandum was a table created by me, where I noted the date and time of the call, the person who I talked to, the synopsis of conversation and other comments, if applicable.

The proposal analysis was a slow process. In first place the contact was made during the summer holidays, which delayed the process. In addition, most hospitals do not have a specific department related to clinical trial, so they did not have a qualified person to evaluate the proposal. However, with determination and persistence Blueclinical increased the network of hospitals.

Apart from the phone calls, I also prepared or reviewed the draft version of financial agreement between Blueclinical and each Hospital.

Business development helped me to improve communication skills, because I made a lot of phone calls. During the calls I always had to be very polite and at the same time I had to put some pressure on the Chairman. It was also a good experience to realize how different the internal procedures are at each Portuguese hospital.

3. DISCUSSION

When my internship started, Blueclinical was a recent company and was not prepared to conduct clinical trials, so the first tasks assigned to me were not related to the job description of CTA. As stated, I contacted suppliers to buy clinical and laboratory equipment. Contacting suppliers helped me to improve my communication skills because I performed phone calls, I sent emails and I also had meetings with suppliers. In these communications I had to make myself clear to avoid misunderstandings, I had to be formal, polite and also had to be influencing to ask for discount in the final price. During this task the biggest difficult that I felt, was asking quotation for equipment that I did not know the recommended characteristics. So, before making any phone call and asking for quotation, I performed my own research about equipment, thus I felt more comfortable with the theme.

Apart from Blueclinical Phase I, I also performed phone calls to Hospitals to expand the network of Blueclinical CRP. This task of business development helped me to improve communication and organizational skills due to the phone calls performed and the record of it on the *memorandum* of phone call, created by me.

During this initial phase, I also helped to write and review Blueclinical SOPs. Although I had already written SOPs during the master course I felt some difficulties in this task because in my previous experience I wrote SOPs with fictitious information. At Blueclinical, SOPs contained "real information" that after approval would be used for consulting, so the responsibility of writing them correctly was bigger. In order to do a better work, I decided to read the master SOP that defined how to write a SOP in Blueclinical, and I also read others SOPs to be familiarized with sentence construction.

These first functions helped to improve all of my training objectives related to "soft skills" that were defined before the internship initiation. I had improved my organizational skills such as multi-task and time management due to have more than one task to do and I enhanced my oral and written communication due to phone calls, emails and documents writing. These functions also helped me to develop my proactivity and influencing skills.

After the initial preparation of the Unit, I started performing specific duties in the area of clinical trials. Since my first role in this field was the submission of clinical trials to competent authorities, I had to deepen my knowledge about Phase I and BA/BE trials. These trials have very specific characteristics that make them totally different of the others phase's trials. As stated before, the trial designs are similar, however each protocol have to be strictly followed. My internship in Blueclinical Phase I gave me the chance to have training in an area of interest underdeveloped in

Portugal, but with a great potential to be developed. In this way, I became one of the reduced number of Portuguese persons with training/knowledge in Phase I.

Clinical trial submission was one of the most enriching experiences during the training, because I had to be highly organized and with a high concentration capacity to assure that all documents will be available at the planned date. I also had to assure that QC of the documents were performed and they were submitted without mistakes. During this activity, I felt some personal difficulties such as organizational competencies, because a clinical trial submission requires an extensive list of documents that were available at different times. I solved this difficulty by creating a list of required documents and I used a "colour code" to identify the documents that were already available (no colour); missing but already in a draft version (highlighted yellow) and documents that are missing and there is not a draft version (highlighted red). In addition to this, sometimes the final versions were update, and a new version of the documents were created. So, I had to remove the outdated version and to file the final and corrected version. This procedure is crucial to assure that a correct version is submitted. Besides my personal difficulties, I also had interpersonal difficulties, because I had to request documents to other persons, such as the sponsor of the trial and other divisions of Blueclinical such as medical writer, data management, business development, research pharmacist, the clinical director and PI. These communications sometimes were complicated, because I had to assure that documents were available with no mistakes in the planned dates. The collaborators were usually very busy, so I had to be persistent with regular communications to insist about the importance of receiving those documents. At the end of my internship, I am glad to say that I never delayed a submission due to Blueclinical collaborators fault, if a delay occurred it was not a responsibility of Blueclinical.

After the submissions, further communications with CA were mandatory. In the beginning of my internship, the CRM was the liaison with them. During this period, I gain experience in this field because I attended to the phone calls with CA and I also read the correspondence. Considering the temporary absence of CRM, I quickly became a liaison with CA, because I was the second person more involved in the CA submissions. During the first times as liaison with authorities I asked myself if I was prepared for that responsibility, because I had a short training in this field. In the following submissions, I was supported by other Blueclinical members that revised some documents before the submission and performed QC of the submission dossier. Quickly, I gained autonomy and self-confidence which made me realize that I was able to assume the role of CA submissions, so I must consider that I achieved two of my secondary objectives.

After the first trial approval by the three CA, Blueclinical conducted its first trial. Before the trial initiation, CRM gave me theoretical training about the steps of trial conduction. I already had research data about Phase I trials, however the "practice details" about the trial conduction is crucial to ensure that everything is performed correctly. After the explanation I still very anxious, because the procedure was a complete new reality for me. The first step was to recruit volunteers by phone calls. This procedure required professionalism and ethical performance, because I had to share the correct data and had to clarify volunteer doubts, however I could not influence volunteer to participate in the trial. In the first calls, I was nervous because I was afraid of providing wrong or confusing information to the volunteer. However with practice I gained self-confidence and started to feel more comfortable during phone calls. With practice I also defined a strategy that helped me to conduct a better recruitment.

Related to trial conduction, screening, admission, confinement phase and end of study everything was also new me. My functions as CTA during the trial conduction were well defined, which helped me to know what my responsibilities were. The first impact was the screening, because it was the first meeting with volunteers, and I had to welcome the volunteers and to help them feel comfortable in Blueclinical facilities in a professional way. During these steps, I had to archive the signed ICFs in the TMF, and I had to review the SD to assure that all data were recorded and all the fields were signed and dated. Conducting these activities simultaneously was confusing and it required a high concentration, so I trained my multi-task and organizational skills.
Apart from the tasks related to the job description of CTA, I undertook other duties such as Data Entrée, which developed my critical thinking and monitoring skills during the data entrée procedure, because I revised SD and the data recorded. The opportunity of processing samples appeared due to a lack of laboratory technician in the first trials, and taking into consideration my bachelor course. This task also gave me more knowledge about Good Laboratory Practices and also helped me to work under pressure, because there were strict times that had to be respected, causing protocol deviations if they were not complied. I enjoyed performing this task, because it was a positive experience, however I do not want work as a laboratory technician in the future.

The nine submissions performed and the five clinical trials conducted during my internship, gave me the necessary training to understand the activities underlined in the Phase I clinical trials. I developed my competences in perform CA trial submissions, manage all documents of clinical trial (including SD and TMF) and also at the conduction of a trial including all the procedures since the recruitment until the discharge. The first conducted trial was an adventure, the second was a test,

and the third a confirmation that I was capable to perform functions as CTA. The following trials conducted during my curricular internship worked always as different training with real-situations. During the initial months of my internship I learned with CRM some skills and characteristics of a project manager, such as communication, organizational and problem-solving skills. Once again, due to the temporary absence of CRM, someone had to assume functions as project manager, and I was one hypothesis because during the internship, I showed my competences in different tasks and my behaviour in various situations. Acting as project manager was a big challenge, taking into consideration the responsibility of the job and my shorter experience in this field. The biggest difficulty that I felt was communicate by email with trial sponsor, because sometimes I had doubts about how I should write, mainly if the emails were written in English, since the documents will became a legal support of how the events succeed, and can be used against company. Other barrier felt was to be informed about all details and the project status of each trial. In order to keep me updated, I created an excel table for each trial where I registered every information, for instance date, name of person/entity and the activity performed. With this tracking tool, I could rapidly find information that I needed. It is important to sum that the Clinical Operations Manager, who clarified all my doubts and helped me to made decisions, always supported me. Blueclinical gave me an incredible opportunity to grow and develop several competencies by acting as project manager. At the end of the internship I felt a big growth, however I still feel that I needed more training with real situations. Although all projects were moving well, I was afraid that a situation could appear that I was not capable to solve. So, I must can conclude that I achieved the objective that I defined in the beginning of the internship, of act as project manager, however I still have a lot to train.

Along with specific training, I performed other duties that complemented my training. I wrote and revised CTPs and ICFs which developed my written skills, and it also helped me understood that the Medical Writing was not an area of interest to me. Relating to SOPs, the situation is similar to medical writer, because although I did not felt big difficulties, I conclude that is not an area of interest for me. The activity of writing SOPs and the entire internship in Blueclinical, helped me to realize how a Quality Management System is organized and how it works. This training helped me to realize that write a SOP can be a task assigned to me because I am capable to perform it, however I do not imagine my self-having in future functions related to the Quality Management System because it is a methodical process.

The monitoring visit to the hospital, in the context of Blueclinical R&D granted me the chance to see how it is a working day of monitor in a site, which allowed me to meet other job related functions to my working area. During the monitoring visit I had the opportunity to see different

documents and trial procedures from Phase I, and also to know a different reality from the "controlled world" that Phase I is.

The tasks performed in the others divisions of Blueclinical enriched my training considering the multidisciplinary tasks assigned and the improvement of my soft skills and enlargement of my knowledge about clinical research. They also helped to realize that my profile is more appropriate for Phase I Unit functions and as project manager.

Taking into account the tasks that were assigned to me and the responsibilities that I assumed during the internship, I am thankful to Blueclinical management for the opportunity they gave me and also for the confidence they placed in me.

4. CONCLUSION

During the internship I had the opportunity to work in a young Portuguese company, with different units of business related to clinical research. This particular characteristic of Blueclinical, gave me the chance to have a transversal training at the different units of business R&D, CRP and Phase I which gave me a general vision of company operations.

The multidisciplinary activities performed in the context of Blueclinical divisions enhanced my background in clinical research, my capacities of medical writer, as well as a number of soft skills. Regarding the latter, during these 10 months of internship, I felt a huge improvement of my capacity of concentration, multi-task and time management skills, since I had to perform different tasks at the same time. Considering that I communicated with a wide range of entities, such as sponsors, volunteers, suppliers, CA and other Blueclinical collaborators, I noticed a substantial improvement in written and oral communication. The unexpected situations stimulated my proactivity and problem solving skills, because I tried to make a suggestion for resolution when I had to ask for help.

Considering duties of medical writer and SOPs writer, they enriched my theoretical knowledge, and helped me to improve my written skills and to realize that they were not my favourite tasks.

Regarding my specific training, I acquired knowledge of Phase I and BA/BE trials conduction, and related regulations and guidelines. I had the opportunity to submit 9 applications for CA approval, which gave me a considerable experience in the activity. Concerning the trial conduction, I had the opportunity to participate in 5 BA/BE trials which I consider a significant number taking into account that Phase I Unit started functions recently. Although BA/BE studies design are similar, I was challenged with different situations during the trials conduction, which worked as "stress-test" and also enhanced my experience.

My experience as project manager had a lot of importance to me. Considering my short experience and all the unexpected situations that can appear during a project, I think that in this moment I am not yet sufficiently autonomous to embrace the whole responsibility. However, taking into account the challenges of this job, and my personal characteristics, I really see me myself in the role of project manager in future.

At the end of this internship I concluded that all the training objectives were successfully achieved. I can also conclude that CA submission and project manager are the areas I intend to continue to develop in the future, because the success is the result of hard work, learning from failure and persistency, but it is only achieved if we like what we do.

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