Universidade de Aveiro
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Secção Autónoma de Ciências da Saúde

PAULA CRISTINA LEÃO MOREIRA

RELATÓRIO DE ESTÁGIO NA UNIDADE PHASE I DA BLUECLINICAL

INTERNSHIP REPORT ON BLUECLINICAL PHASE I UNIT

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do professor Doutor Bruno Miguel Alves Fernandes do Gago da Secção Autónoma da Saúde da Universidade de Aveiro e da Doutora Cristina Manuela Pinto Vieira Lopes, Diretora de Operações Clínicas da Blueclinical.

Dedico este trabalho aos meus pais e namorado pelo incansável apoio.

o júri

presidente	Prof. Doutor José Luís de Almeida professor associado da Secção Autónoma de Ciências da Saúde Universidade de Aveiro
vogal – Arguente Principal	Prof. Doutor José Carlos Fontes das Neves Lopes professor auxiliar da Secção Autónoma de Ciências da Saúde Universidade de Aveiro
vogal – Orientadora	Doutora Cristina Manuela Pinto Vieira Lopes diretora de operações clínicas e desenvolvimento de negócio da Blueclinical Lda.

agradecimentos

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À Universidade de Aveiro, academia do meu coração.

À organização e direção do Mestrado em Biomedicina Farmacêutica, que me mostrou um novo caminho profissional muito do meu agrado.

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Ao Guilherme, por tudo.

Aos meus pais, pelo amor incondicional.

palavras-chave

Investigação Clínica; Biomedicina Farmacêutica; Indústria Farmacêutica; Ensaios Clínicos; Fase I; Biodisponibilidade; Bioequivalência; Voluntários Saudáveis.

resumo

Ensaios clínicos de Biodisponibilidade/Bioequivalência são uma área promissora em I&D Farmacêutico, e é muito interessante estar envolvida neste âmbito. Durante o estágio pratiquei atividades de assistência a ensaios clínicos de Biodisponibilidade/Bioequivalência sendo este o meu alvo de intervenção na Blueclinical durante dez meses. Durante este tempo também tive oportunidade de exercer atividades de enfermagem de investigação devido à minha formação anterior na área.

Este relatório tem como objetivo descrever as atividades em que estive envolvida, os pontos de aprendizagem e a experiência adquirida em relação à condução de ensaios clínicos de Biodisponibilidade/Bioequivalência.

Durante o estágio desenvolvi atividades de assistência de ensaios clínicos e aprendi muito sobre o processo de condução do ensaio, desde a submissão do ensaio junto das autoridades para obter a sua autorização até ao processo de relatar os resultados.

Este trabalho foi um desafio e um processo de aprendizagem contínua. No final desta etapa, sinto que foi um esforço recompensado e desejo continuar a desenvolver as minhas capacidades nesta área.

keywords

Clinical Research; Pharmaceutical Medicine; Pharmaceutical Industry; Clinical Trials; Phase I; Bioavailability; Bioequivalence; Healthy Volunteers.

abstract

Bioavailability/Bioequivalence clinical trials are a promising area in Pharmaceutical R&D and it is very interesting being involved in this field. During the internship, I practiced assistance activities to Bioavailability/Bioequivalence clinical trials and this was my target for intervention within Blueclinical during ten months. During this time I also had opportunity to exercise nursing research activities due to my previous training in the area.

This report aims to describe the activities in which I was involved, the learning points and the experience achieved about the conduction of Bioavailability/Bioequivalence clinical trials.

During the internship I have developed clinical trial assistance activities and I learned a lot about the process of trial conduction, from the submission to the authorities to get their approvals until the process of reporting the results

This job was a challenge and a continuous learning process. At the end of this period, I feel it was a rewarded effort and I would like to keep developing my skills in this area.

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Abbreviations

AUC	Area under the plasma drug concentration-time curve
BA/BE	Bioavailability Bioequivalence
BLCL	Blueclinical
CA	Competent Authority
CEIC	*Comissão de Ética para a Investigação Clínica* - Ethics Committee for Clinical Research
CFR	Code of Federal Regulations
Cmax	Maximum drug concentration
CNPD	*Comissão Nacional de Proteção de Dados* - National Commission for Data Protection
CRF	Case Report Form
CRM	Clinical Research Manager
CRP	Clinical Research Partnership
CSR	Clinical Study Report
CTA	Clinical Trial Assistant
CTP	Clinical Trial Protocol
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
IATA	International Air Transportation Association
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IMPD	Investigational Medicinal Product Dossier
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde* - National Authority of Medicines and Health Products
NHS	National Health System
RN	Research Nurse
SOP	Standard Operating Procedure
TMF	Trial Master File
USA	United States of America
WMA	World Medical Association

1. Introduction

This report aims to describe my curricular training in order to complete the Training Programme in Pharmaceutical Medicine and obtain a Master Degree in Pharmaceutical Medicine.

I have been in Blueclinical Phase I Unit as a Clinical Trial Assistant (CTA) trainee for ten months, since 3rd September, 2013. During this time, I also had the opportunity to perform some nursing activities related with Phase I Clinical Research because of my background of Licensed and Registered Nurse.

Globally, I would like to expand my knowledge in clinical research, but more specifically on Phase I clinical trials activities. Also, if needed, combine two roles, CTA and Research Nurse, alternating between one and another, but essentially I aim to gain experience in clinical trial assistance.

At the next point I will identify the objectives I proposed myself to reach during the internship, dividing it, in two sections: as CTA and as Research Nurse, but as I said before I will give more relevance to the CTA role.

1.1. Training objectives

As a Clinical Trial Assistant,

- Acquire competencies to contribute to the review of protocols and other study related documents;
- Develop my communication skills, communicating with sponsors and study teams;
- Improve my knowledge and capacity to apply International Conference of Harmonization - Good Clinical Practice (ICH-GCP) and Helsinki Declaration on my daily work conduct;
- Learn that clinical trial procedures are performed in compliance with study protocols, national policies and standard procedures, GCP and applicable regulatory requirements in the Unit;
- Know better and apply legislation (either national or international legislation, European and ICH-GCP guidelines for the management of clinical trials and mechanisms for licensing of products) applicable to clinical research activity;
- Learn how to create strategies to organize the agenda and efficiently be compliant with the defined deadlines;

- Provide assistance to clinical staff by organizing files, projects, data, etc. and be responsible for general office management to keep operations running smoothly;
- Understand how to assist the development and execution of clinical trials;
- Assist with routine data verification and quality control, ensuring data integrity and consistency with prescribed study protocol;
- Improve my performance of literature searches, research, and overall administrative assistance;
- Learn how to ensure worksheets are correctly completed by staff and pre-dose activities are finalized on time before dosing occasions;
- Continuously assess and suggest improvements for clinical operations processes to ensure safety of study participants and delivery of high quality data;
- Contribute to data entry and Case Report Form (CRF) completion;
- Participate in the development, review and revision of Blueclinical SOPs and policies;
- Contribute to risk assessment and management and support the Quality Manager.

As a Research Nurse,

- Carry out clinical study procedures during screening, dosing and discharge, ensuring and monitoring safety and wellbeing of study participants (healthy volunteers);
- Carry out clinical activities in the Unit and screening area such as venepuncture, ECGs, vital signals monitoring, and other protocol specific assessments;

For both of these functions, at the end of this period, I would like to perform the different tasks autonomously, be able to maintain the unit calm and organized, and regularly perform self-evaluation and try to improve my professional performance in order to contribute to high quality clinical research.

This report is structured in 6 chapters. Chapter 1 presents the introduction where are listed my personal training objectives. Chapter 2 includes an overview of the host institution – Blueclinical. The state-of-the-art is placed in Chapter 3. Chapter 4 describes the tasks I performed during the training. The tasks are divided in two main sections, multidisciplinary and monodisciplinary training. The last two chapters, 5 and 6, relates the discussion and conclusion, respectively.

2. Overview of the host institution – Blueclinical

Blueclinical operates in three different areas: Blueclinical Phase I; Blueclinical Clinical Research Partnership (CRP) and Blueclinical R&D.

Observing the Blueclinical organogram, (Appendix A) illustrates the relations between people within the different departments. It also enables to visualize the complete Blueclinical structure and organization.

2.1. Blueclinical Phase I

Blueclinical Phase I was inaugurated at July 12, 2013 and it aims to conduct of Phase I studies in healthy subjects and early proof-of-concept studies in selected patient populations. This is the area where I was allocated to conduct my role as CTA.
Phase I studies in healthy subjects are performed in an exclusive and dedicated 29-bed unit located at Hospital da Prelada, Level 3, Oporto, Portugal, with appropriate facilities to the clinical trials conduction. The team has physicians, nurses, pharmacist, clinical trials assistants, laboratory technicians and project managers working on planning and conduction of Phase I clinical trials (1).

2.2. Clinical Research Partnership

Clinical Research Partnership (CRP) supports and collaborates with clinical research centers, promoting their growth, efficiency gain in clinical research sponsored by the pharmaceutical and medical devices industry or investigator-driven (1).

CRP is a growing network of hospitals and primary care centers that serve a significant percentage of the Portuguese population. The full network operates under a common quality management system to create value in clinical research.

2.3. R&D Consultancy

Blueclinical R&D aims to provide expert advice on clinical research opportunities resulting from “translational medicine”. It can also prepare and implement all the phases of development plans of news drugs, medical devices and other health products.

There are other activities, such as: preparation and monitoring of scientific and regulatory advice; planning and supervision of pharmaceutical development and analytical methods; preparation of the investigator’s brochure and the investigational medicinal product dossier (IMPD); portfolio selection support and analysis and support in the preparation of the business plan and application for funding (1).

3. State-of-the-Art – Pharmaceutical R&D and BABE clinical trials

During the training I was dedicated to learn, mostly, about BABE clinical trials conduction, for this reason, this chapter is dedicated to this topic.

3.1. Pharmaceutical R&D overview

Science and technology advances are leading to new research methods and promising expectations for the future. Pharmaceutical R&D also contributed to a life expectancy increase, up to 30 years longer than a century ago to European Union (EU) citizens (2).

Over this time, the process of R&D and the industry have changed their strategies from the blockbusters[1] (3) approach to a more specific and specialized approach where the clinical trials are more rigorous and cost-effective designed(4). To reach these goals, some of the strategies taken were related with regulatory aspects, which directly influenced the companies' organization/structure, processes and strategies, so it is crucial and challenging to a company to be compliant with these requirements and follow the most updated guidelines (5, 6).

EU and United States of America (USA) legal framework for medicinal products for human use can differ in some aspects, for example, USA is quicker regarding the regulatory aspects (7), but both agencies aim to ensure a high level of public health protection and to encourage innovation, and are responsible to concede the marketing authorization (8).

Despite the changes that were implemented, the Pharmaceutical R&D is still a long (almost 4 years, see Figure 1), expensive (see Figure 2) and complex process. To reach the success, most of the times, there were plenty of failures before (9).

[1] Blockbusters drugs are generally defined as drugs that solve medical problems common to hundreds of millions of people and, at the same time generate large sales increases and profits for the pharmaceutical companies.

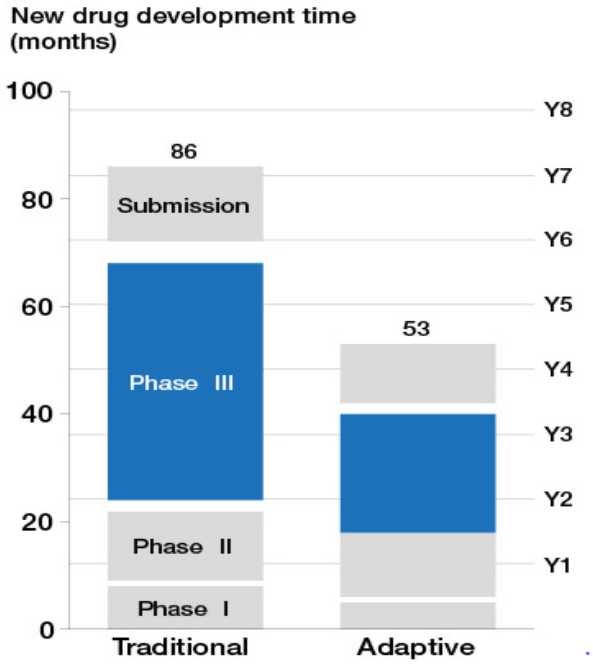

Figure 1 – New drug development time (months) comparing a traditional and an adaptive approach. Available from: The World Economic Forum, 2013 (9).

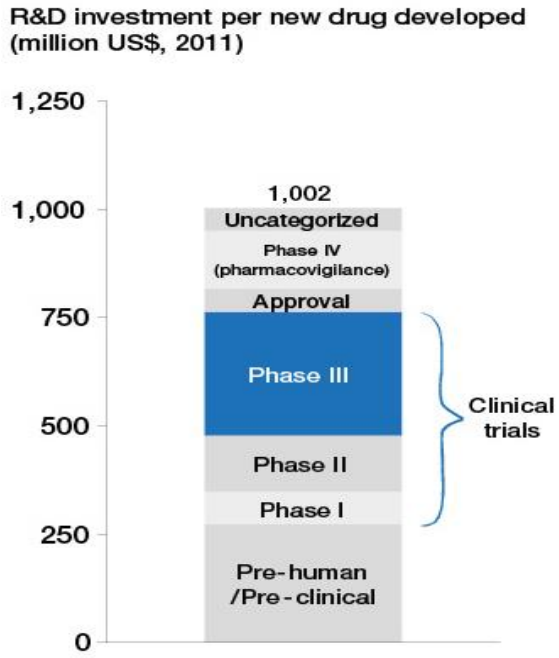

Figure 2 – New drug development costs (millions US$) per phase. Available from: The World Economic Forum, 2013 (9).

US and EU, perform most of the clinical trials, although with the recent international harmonization of procedures and the standardization of the requirements, some countries, called emerging regions, such as Eastern European, Latin American and Asian countries are now increasingly

receiving industry-sponsored clinical research as it is presented in Figure 3. This opposes the trend of the traditional places such as North America, Western Europe and Oceania. Now, developing countries are more attractive because of their lower cost per patient which leads to increased economic profits (9).

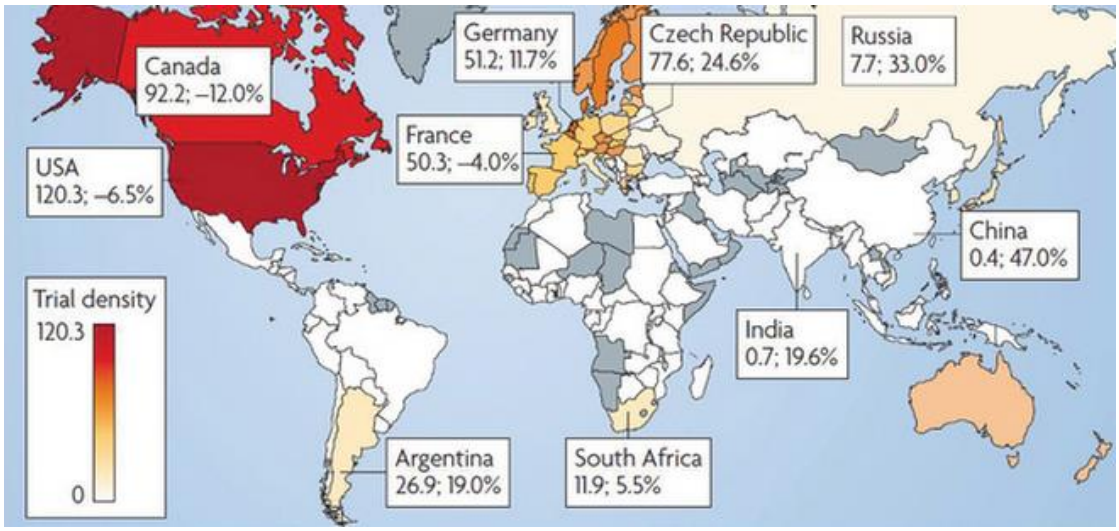

Figure 3 – Trial density is indicated by color, with the darker color having higher densities. Annual growth rate is indicated for some countries. Available from: Thiers FA, Sinskey AJ, Berndt ER, 2008 (10).

It is also interesting to look at the numbers for positive opinions released by the European Agency of Medicines (EMA) concerning medicines for human use, Figure 4, shows an increase from 57 positive opinions in 2012 to 81 positive opinions in the past year. In accordance with Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use (CHMP) is the responsible body inside the Agency to answer the questions concerning medicines for human use (11).

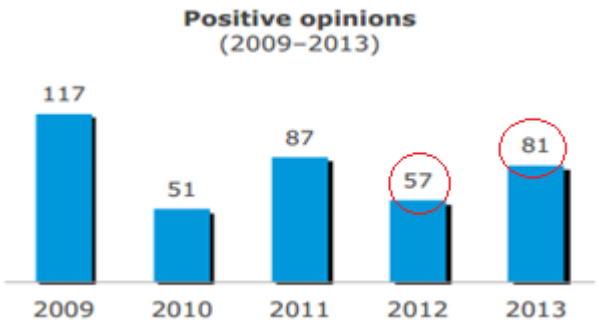

Figure 4 – CHMP opinions for medicines for human use, since 2009 until 2013. Adapted from: European Medicines Agency – EMA, 2013 (12).

The challenge is to understand the need of new treatments or the need of improving the existing ones, expanding the scientific knowledge and its complexity, and be competitive with the developing markets (13).

3.2. Phase I to IV and Bioavailability and Bioequivalence Clinical Trials Worldwide

Clinical trials and the process of clinical development of pharmaceuticals for human use can be divided in four temporal phases (I-IV) (14):

Phase I

This phase respects to the first administration of a new drug into humans. At this phase of development, a small group of people is involved, usually 20 to 80 participants, these participants are usually healthy volunteers. The objective is to evaluate safety, determine a safe dosage range, and identify side effects (14).

Phase II

"*Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients."* in General Considerations for Clinical Trials, ICH-E8 (14). The number of participants is usually 100 to 300 (15).

Phase III

"*Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population."* in General Considerations for Clinical Trials, ICH-E8 (14).

Involves a large population in study, the number of participants can reach to thousands (1000-3000) (15).

Phase IV – Post -Marketing

It involves the safety surveillance (pharmacovigilance) starting after drug approval. This type of trial aims to provide additional information on longer-term safety and side effects and also are useful for optimize the drug's use or to test the product in different populations of people, such as children (14, 15).

Bioavailability and Bioequivalence (BA/BE)

During the internship I participated in several BA/BE clinical trials, and therefore, the report will focus on this subject.

BA/BE clinical trials are a growing market due the patent expiring in the next years (10, 16).

BA/BE trials were first established in 1984 by The Drug Price Competition and Patent Term Restoration Act, informally known as the "Hatch-Waxman Act" [Public Law 98-417], this is a federal law in United States which encouraged the manufacture of generic drugs by the pharmaceutical industry and established the modern system for government generic drug regulation (17).

Bioavailability is defined in Code of Federal Regulations (CFR) 320.1 as:

"The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action."(18).

Bioequivalence is defined in CFR 320.1 as:

"The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."(18).

To get approval for generic medicines the most important parameters evaluated are: 1) bioequivalence (defined above); 2) maximum drug concentration (Cmax) is the parameter used to characterize the absorption rate and 3) the area under the plasma drug concentration-time curve (AUC) is the parameter used to characterize the extent of drug absorption. Comparing the test and the reference drugs, Cmax and AUC are restricted to vary within a certain limited range to be approved as a generic version (19).

In terms of numbers, Figure 5 shows that the healthy, diabetes and fasting/ fed conditions are the most commonly researched conditions among bioequivalence and bioavailability studies registered in ClinicalTrials.gov (20).

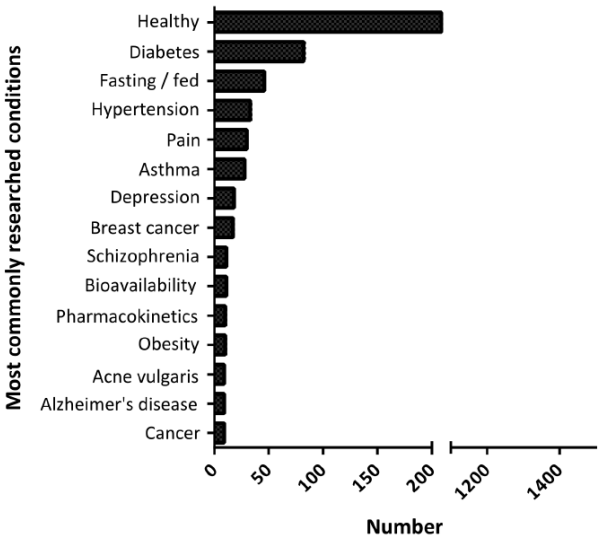

Figure 5 – Most commonly researched conditions Adapted from: Spigarelli MG, Stockmann C, 2013 (20).

As mentioned above, the migration of the industry-sponsored clinical research to emerging countries seriously affected BA/BE clinical trials market, constituting a huge competition in the marketplace with very competitive prices compared to those prevailing in developed countries (9).

The global distribution of ongoing bioequivalence and bioavailability trials is shown in Figure 6. This figure shows that the majority of the BA/BE trials are being conducted in North America, however East Asia, Middle East and South America also have ongoing bioequivalence and bioavailability trials (20).

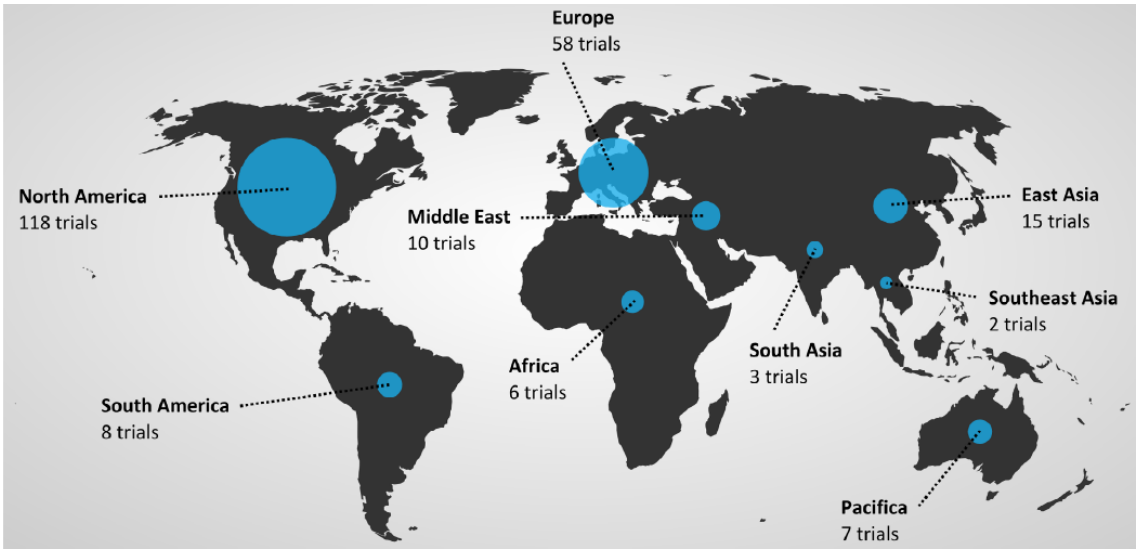

Figure 6 – Ongoing Bioequivalence and Bioavailability Trials Registered in ClinicalTrials.gov between 01 October 2007 and 31 December 2012. Adapted from: Spigarelli MG, Stockmann C, 2013 (20).

The pharmaceutical industry will continue to face changes and challenges, regarding global economic uncertainties and the increasing spending on pharmaceuticals. These changes will modify the global pharmaceutical prospect, which must increase productivities and improve efficiency (20).

The spending on pharmaceuticals over the next years tends to continue to increase, because of the growing use of medication and population, as global population raises. The next years will have a big number of patents expiring, leading to an increase of the generics market (16).

3.3. Phase I Clinical Trials in Portugal

The number of undergoing clinical trials in Portugal between 2006 and 2013 fell 28.75%, from 160 to 114 studies (see Figure 7). The lowest number of clinical trials submitted in Portugal since 2006, was reached in 2011, with only 88 studies (21).

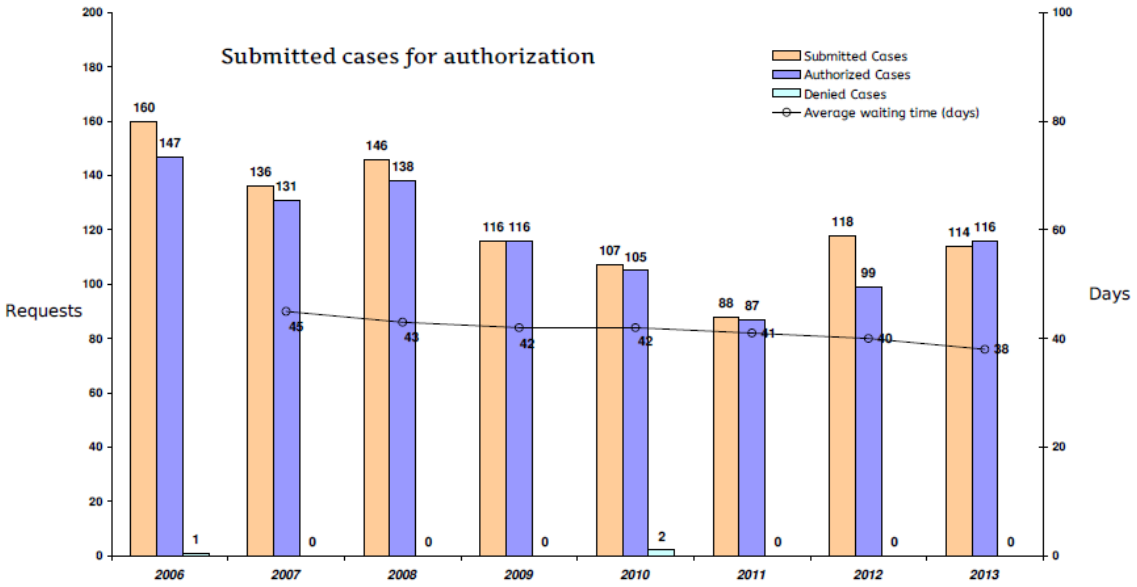

Figure 7 – Submitted cases for authorization (2006-2013) – adapted from INFARMED website (22).

During 2013, ten (10) Phase I clinical trials have been submitted and validated by INFARMED (22), and Blueclinical was responsible for five of them, these were clinical trial applications of BA/BE clinical trials.

shows the number of Phase 1 clinical trials submitted and validated since 2005 until last year.

Table 1 – Number of Phase I Clinical Trials submitted and approved since 2005 Available from: INFARMED website (22).

2005 (2nd sem)	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
3	2	7	3	6	2	6	3	10

In this moment of economic crisis that Portugal is going through, and to rationalize the use of drugs in financial terms, generic drugs emerge as an opportunity due to its lower cost. In Portugal, the proportion of generics has increased steadily, approaching in August 2013, 40% of medicines reimbursed by National Health System (NHS) and this percentage is intended to be expanded to 60% in 2014 (23). Regarding this, Portugal would benefit from better use of national capacities for clinical research, specially this growing generic market, but to achieve this, we need to improve some aspects related to planning and project management, and reduce the administrative complexity (24, 25).

4. On-the-Job Training

4.1. Multidisciplinary training

In this section I will describe the generic skills to better play my role, for example, the understanding of the main regulations and legislation applicable to clinical research, the Helsinki Declaration and the reading and understanding of Standard Operating Procedures related to Blueclinical activities.

4.1.1. Regulations and legislation

The pharmaceutical industry is highly regulated and Phase I clinical trials are not an exception. Drug development has been suffering changes to improve the process, these changes include, mainly regulatory aspects and the increase of transparency in the drug development.
With the overall aim of harmonizing the procedures for conducting clinical trials with regard to regulatory, scientific and ethical aspects throughout Europe results the Directive 2001/20/EC in 2004, which was transposed into national law of each Member State.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 defines the requirements for the conduction of clinical trials in the EU *"on the approximation of the laws, regulations and administrative provisions of the Member States"*(26).

However, almost a decade after its implementation several opportunities were found for improvements of the current Directive, for example, the transposition for each Member State verifies some discrepancies, increased bureaucracy and hence increased costs.

For these reasons, in July 2012 the European Commission suggested and implemented a proposal for a new European Regulation to replace the current Directive (27).

The Good Clinical Practices (GCP) Directive 2005/28/EC April 8, 2005 results from the Directive 2001/20/EC.

In Portugal Directive 2001/20/EC resulted in Law 46/2004 of 19 August which has recently been replaced by Law 21/2014 of 16 April. GCP Directive 2005/28/EC resulted in Decree-Law 102/2007. Beyond these should always be applied the Law 67/98 of 26 October, on the protection of personal data.

Internationally and according the ICH-GCP, the regulation of all these aspects are harmonized and ensures integration, in a regulatory basis of the principles, guidelines and quality requirements that should govern the conduct of these studies, in order to protect all subjects who participate. These were the main objectives of the extensive legislation that has been recently produced and which is compiled in volume 10 of EudraLex (28).

BA/BE trials to non-EU countries, must comply with the regulations of the different regulatory agencies.

4.1.2. Helsinki Declaration

Nowadays, the ethics applied to research, both to social sciences and biomedical research, unfortunately were built on mistreating human beings and disrespecting ethical values. Nuremberg Code is an example of this, it was created in August 1947, in Nuremberg, Germany, by American judges sitting in judgment of Nazi doctors accused of conducting murderous and torturous human experiments in the concentration camps (29, 30).

The Declaration of Helsinki is one of the major ethical guidelines for conducting clinical research. Along its existence it has been modified in several different occasions and the last version was released in October 2013. The Declaration is an important document in the history of research ethics, and stands as the first major effort of the medical community to regulate research itself. It is considered to be the 1st international standard for biomedical research and is the basis of most subsequent documents (31).

The Declaration of Helsinki has nearly half-century of existence and it defines the Ethical Principles for Medical Research involving Human Subjects, this principles are developed by a medical community - World Medical Association (WMA). The Declaration includes principles on safeguarding research subjects, using correctly the informed consent, minimizing the risks and adhering to an approved research plan/protocol. Declaration of Helsinki and the EU Clinical Trials Directive (2001/20/EC) are fundamental to research governance of clinical trials. Both are applicable to non-commercial (research council, charity-funded) trials and commercial trials (those funded by pharmaceutical companies) (31).

The current version (October 2013) replaces the previous versions (32). The newest version is concerned with the growing clinical research in developing countries and its dangers to their vulnerable populations. And therefore, strives to increase the liability of the sponsors, the

transparency in the disclosure of the results and also that all participants have the opportunity to benefit from the innovative treatments after the end of the clinical trial (33). Also, the new version of The Helsinki Declaration includes, for the first time, the issue of compensation and treatment for participants harmed by participating in research (34).

4.1.3. Standard Operating Procedures

Standard Operating Procedures (SOPs) can be defined as *"Detailed, written instructions to achieve uniformity of the performance of a specific function."*(35) A SOP can have one or several support documents, also known as SuDocs, and it can be defined as documents used to complete or record an action described in the SOP to which it is associated, or as a stand-alone document for a specific activity. The SOP's creation is based in the local law and applicable regulations. All the Blueclinical players of a specific procedure should follow the applicable and most updated version.

One of the first tasks I had when I arrived to Blueclinical was the SOP's reading to better understand the functioning of the unit, and definitely it was a good help, because it provides a wide perspective about how things work or should work.

SOP is not rigid, so after the SOP implementation some aspects can change, and if applicable, the SOP can be updated. Quality control is a constant to keep the SOPs updated and according the needs and the established practice. The introduced changes can be simple administrative changes or critical changes requiring the compliance with a new/updated international or local regulatory requirement, or to address an audit or inspection finding. In both cases an intervention is required, and all the interveners are requested to be aware of the change, and act according the latest version. SOPs are important because it ensures that all research conducted within the Blueclinical follows the applicable regulations, ICH GCP, and institutional policies to protect the rights and welfare of human study participants. SOPs can also be used as a guide to explain how research will be conducted within the Blueclinical and provides an excellent training tool for new employees.

My intervention in this area was related with some updates. Some were related to clinical procedures and others to clinical trial operations and some new SOP's creation of clinical procedures, then submitted to revision and approval. I was more active regarding to SOPs related to clinical procedures due my background, but I also had the opportunity to collaborate in some updates of SOPs related with clinical trial operations and activities.

4.2. Monodisciplinary training

In this section I will illustrate the specific tasks that I performed along the training. I will describe mainly my experience as Clinical Trial Assistant, that was my principal intervention, but also a few tasks performed as Research Nurse.

4.2.1. My experience as Clinical Trial Assistant

Since the training started I have already actively participate in several BA/BE clinical trials, the activities I could perform are described below.

4.2.1.1. Clinical Trial Activities

4.2.1.1.1. Clinical Trial Applications

In accordance with the Directive 2001/20/EC, before submitting an application to the Competent Authorities (CA), it must be obtained a unique EudraCT (European Union Drug Regulating Authorities Clinical Trials) number from the EudraCT database. In order to obtain the EudraCT number automatically the database needs some few information, such as, requestor's organisation name, town/city and country; Sponsor's protocol code number; requestor name; e-mail to which the EudraCT number will be sent; security code; whether the clinical trial is contained in a Paediatric Investigation Plan (PIP); whether the clinical trial will be conducted in a third country (outside of the EU/EEA); and the Member States where it is anticipated that the trial will be run. During the training I had the opportunity to participate and understand how this process works and how the number is obtained, I found it very easy and quick.

After the clinical trial has a EudraCT number allocated, a clinical trial application (CTA) must be filled, this is a unique, EU-wide clinical trial application form provided for and published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the EU. CTA is filled carefully to avoid mistakes and reviewed by at least a second person, performing Quality Control. In Portugal the form is submitted in paper, so the full clinical trial application form is saved as an XML file and submitted on a CD-ROM with several other submission documents.

The submission consists of a valid request for authorization to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial. In Portugal, the competent authorities that must authorize the clinical trial are: National Competent Authority - INFARMED,

Ethics Committee - CEIC and National Commission for Data Protection, *Comissão Nacional de Proteção de Dados* - CNPD.

The procedure is quite identical with regard to both the (INFARMED) and the (CEIC)(36). Both these authorities provide the structure of the contents that an application must contain to be validated, which includes a large organization of documents related to the trial. This structure is available on INFARMED and CEIC webpages.

Regarding the confidentiality and data collection during the trial, the data protection authority CNPD must also give their authorization. CNPD submission it is usually done first because they request less information than INFARMED and CEIC, and the submission follows an electronic format.

After the submission, the process must then be validated, and after the expert evaluation and a plenary meeting, and according the meeting agreements, an authorization can be issued. During this process, the authorities are able to raise questions that should be answer as soon as possible in order to do not delay the procedure of authorization. In case of substantial changes (amendments), the authorities must be informed, during all the time of the lifetime of the trial (submission until LPLV). In case of a non-substantial amendment the sponsor do not need to notify the CA, but the information should be available in the trial documentation. (see Figure 8)

To define an amendment as substantial or not (37), depends if the amendment is likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial.

I followed several submissions to the competent authorities and I could understand the granularity of the submission documents and the specific requests from the different authorities. It is a process that requests good organizational and management skills, because the in charge person must collect all the necessary documents and organize them according the provided structure from the authorities. So, being able to participate in this task allowed me to improve the organizational competency and at the same time, I learned, in detail, the steps of the clinical trial application to a national level.

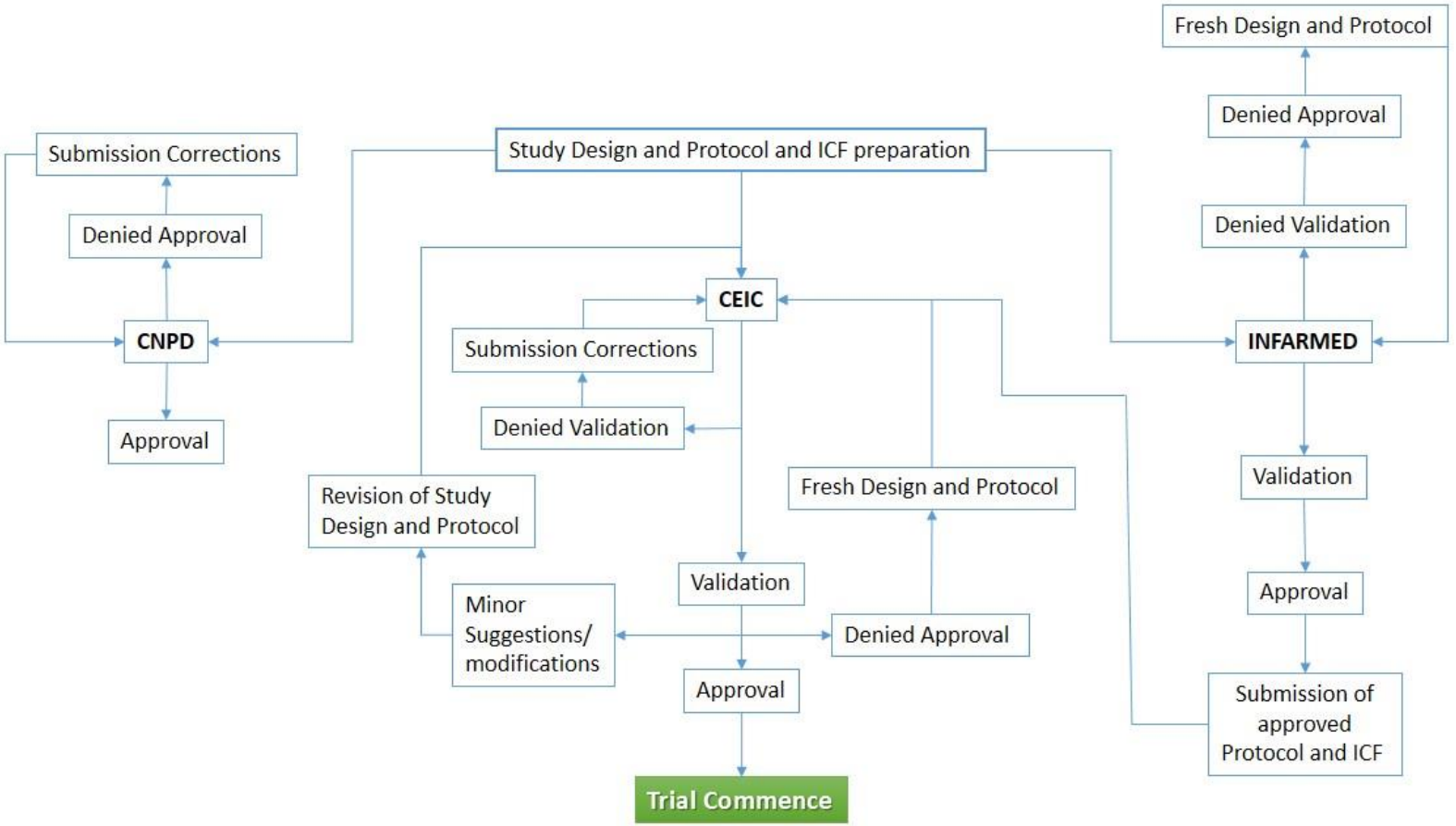

Figure 8 – Competent Authorities Submission Process - Portugal

4.2.1.1.1. Trial Master File (TMF)

TMF is a document that goes along the clinical trial and retains relevant information related with the trial. It works as a standard, central and orderly filing system which allows the effective storage and location of the large volume of regulatory and approvals documents needed for clinical research (38).

The European Directive 2005/28/EC describes the TMF as *"essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated".*

These essential documents are defined by ICH GCP, Section 8.1 as those that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

I contributed to the TMF construction during the trials I had participated. I learned that the TMF must be updated on an ongoing basis to ensure it is always audit and/or inspection ready.

As a CTA I had the opportunity to:

- Document management and archiving;
- TMF maintenance until the study is formally closed and allow direct access to all requested essential documents by the monitor, auditor, Ethics Committee or regulatory authorities;
- Verify there are no missing documents;
- Ensure that required essential documents are on file.

TMF should be organized according the applicable directives and guidance aiming to assist with the trial management, GCP compliance and possible inspections. The sites that are responsible for the conduction of the trial must kept a TMF but the Sponsor should also organize their own TMF or might delegate this task to the site.

During the trials conducted in Blueclinical Phase I facilities, I had the opportunity to organize the site TMF in parallel with the Sponsor TMF. Reviewing and confirming that all necessary documents were available for close-out visits and inspections allowed me to get more aware of the essential documents needed. (39).

Blueclinical Phase I has a specific SOP to standardize the table of contents defining the TMF structure, so, at each trial the defined structure is used. The contents' structure was created according the Directive 2001/20/EC.

During this process, I had the opportunity to organize and review several TMF's, and it made me understand its importance. I learned how it is the crucial to future enquiries to the trial. On the other hand I feel that this process could be transformed in an electronic storage that is safer and more eco-friendly.

4.2.1.1.2. Recruitment

Potential trial volunteers are recruited from an electronic database of people who have indicated their willingness to participate in a trial.

The main dissemination strategy for the recruitment of healthy volunteers is the announcement on Blueclinical website where it is provided general information about Phase I clinical trials and its procedures. The potential volunteers can sign up by filling out a form with some personal details (approved by CEIC and CNPD).

Blueclinical methods and strategies used for recruiting healthy volunteers for Phase I clinical trials are defined by the Clinical Research Manager (CRM), as needed. The process ensures specific recruitment of healthy volunteers for clinical trial data in accordance with ethical and legal requirements and with the approval of the CEIC and the CNPD.

I had the opportunity to create several memorandums with the trial details and relevant information, which helped me substantially in the recruitment procedure. It is a useful tool to use when the recruitment is by phone because it is a good guidance. It also helps to communicate relevant information and pre-screening the main inclusion/exclusion criteria to the trial. The memorandum is based on the protocol and the informed consent form and must be approved by Clinical Director (CD) or other person designated by him.

Recruitment requires a good preparation to answer to a different range of questions related with the trial. I spend several hours recruiting volunteers. Each call can only take a few minutes or can be much longer than that, it depends on the knowledge of the person that is listening and the questions asked.

I learned that a good strategy of recruitment by phone is: keep it simple! Detailed information is given at the screening period when all the written information (Informed Consent) is provided to the volunteer.

I had the opportunity to perform this task during the trials I participated, it can be a hard task for several reasons:

- The Blueclinical database is still increasing to be able to provide the number of needed volunteers to participate in each trials, so every recruitment periods were very difficult to reach the numbers of volunteers needed.
- The recruitment is performed by phone, and each call requests different type of communication, the person on the other side of the telephone can question a lot of aspects or do not question anything at all, it is variable. It should be maintained an easy vocabulary but at the same time everyday words can mislead, so I learned we should be transparent but cautious with the vocabulary used to inform volunteers.

Independently of the recruitment method used, the volunteers must be recruited of their own free will. I also had the opportunity of manage the volunteer's database. After the volunteer participate in a clinical trial he must be absent of any clinical trial participation at Blueclinical or other institution for at least 3 months, and during one year can only participate in 2 clinical trials. Blueclinical keeps a record of volunteers who participate to avoid excessive use of any volunteer.

These tasks allowed to achieve the following goal I proposed in the beginning of the training: "Develop communication skills" through the contact with potential volunteers, recruitment by phone, contacting by email and face-to-face.

4.2.1.1.3. Investigator's Meeting

Before the clinical trial begins and after the Competent Authorities approval the Investigator's Meeting takes place. At this moment all team members that will take part of the clinical trial must be present and be authorized by the Principal Investigator (PI) to participate, PI also delegates the tasks that will be performed by each member during the trial according to their competencies.

During the Investigators Meeting it is discussed the protocol specificities, GCP and other relevant documents/procedures related to the trial such as improvements needed, confronted with the last performances. It is like a discussion forum where are debated possible ways to improve performance and crucial points to the trial.

As a CTA I could prepare the meeting support material, make sure all paperwork was correctly signed and dated, including the confidential agreements.

The support material includes the investigators' meeting dossier (hard copy) which contains at least: Protocol; Investigator's Brochure; CRF specimen copy and filling instructions; Clinical trial timelines; GCP guideline; Helsinki Declaration and other relevant documents.

I also should ensure that delegation of study tasks form is accurate and complete at the end of investigators´ meeting and that investigators' meeting related documents are archived in the trial master file (TMF).

4.2.1.1.4. Screening, Admission, Confinement and Follow-up

Once the volunteer arrives to Blueclinical receives some guidance about the screening procedures, also, it is provided the written information (Informed Consent Form – ICF) of the clinical trial. From this moment, at least 30 minutes is given to the volunteer to read all the information. After the volunteers finishes reading and accepts to participate in the clinical trial the volunteer can proceed to the other screening procedures such as, medical examination, vital signs, ECG, blood and urine collection, according to protocol specifications. The investigator should evaluate trial volunteers as suitable on the basis of tests. At the end of the screening visit the volunteer keeps one of the two ICF's that he have signed and dated and the other ICF is archived in the TMF.

According the internal procedure to identify the volunteer, a screening number is assigned in a sequential order, through the day and time of arrival, and three name initials.

During the screening process, a volunteer may not get enrolled into the trial for various causes, for example, the volunteer not meet the inclusion criteria or meet the exclusion criteria (ineligibility). Screening failures must be documented during the screening process.

The screening is a very important moment when the volunteer decides to participate or not, at this time the volunteer receives all written information (ICF's) and have the chance to clarify all their doubts with the team. It also necessary to verify if all documents are properly filled, for example, that the documents are all signed and dated correctly. If necessary, the volunteer can take home an ICF to reflect or discuss with others, and, if they like to, return later.

As a CTA, I am involved in all this process, including:

- the reception and orientation of the volunteer in the unit;
- the delivery and explanation of the latest version of the ICF;
- clarifying doubts;

- conduct them to the Physician and Nurse;
- verify the source documents and ICF's and as well as archiving it on TMF.

Before the volunteer exits the unit, check that everything is signed properly and that all screening procedures were performed as expected.

Upon review of ICFs, I must consider several aspects, such as, the verification if the ICF is identical to the lasted approved version; if all the volunteers who complete the screening signed an ICF; if all of the ICF were dated and signed personally by either volunteer or by the investigator; if the information completed is clear and legible. In case of non-conformities related to the ICF these are discussed with the PI to be resolved adequately.

During all these procedures of handling of trial materials, the data collection are designed to maintain the volunteer confidentiality within the requirements of Good Clinical Practice, Declaration of Helsinki and the trial protocol.

4.2.1.1.5. Source Documents / Case Report Forms (CRF)

Source documents retain all the record data of each volunteer, this document can prove that eligibility criteria are applied as defined by the trial protocol. The trial monitoring / auditing is based on the information stated in the source documents, and through the source documents it should be possible to recreate what happened in a specific situation, so the monitor or auditor can reconfirm the data (40).

The first moment the data is introduced into the source documents is at the screening, after the ICF is signed. After that, the document continues to be filled in until the volunteer completes the clinical trial and all the adverse events, if any, are all resolved and closed. From this data interpretation it will result the final clinical study report (CSR).

The source documents suffered changes since the first clinical trial in Blueclinical, suffering several changes, in order to improve the source documents contents and structure. These changes aimed to facilitate the reporting process and the compliance with the protocol requirements and specificities. The deviations were detected during monitoring visits and quality reviews. Sometimes it can be difficult to transpose the protocol requirements to a document that collects it because of the protocol specificities.

During the clinical trial, as a CTA I could review the source documents in order to verify if the completion was according to the expected, for example, checking if the records were all dated and signed, if there are any missing data, etc. In order to protect the volunteer's rights, safety and well-being and to guarantee reliable results. Again, as a CTA I must ensure that the information in the source documents are accurately reported and are compliant with the GCP's and the Protocol.

Collecting data may seem a very simple task, however, ensure that data are accurate and reliable can be a complex and detailed task. Along the process, it is always necessary to perform quality control, and then the monitors can also perform quality auditing, raising queries as needed. Data management performers also launch queries, waiting for our answer of their questions. I had the opportunity to enter data from source documents into databases, detect errors or queries raised and find the answer to solve them.

I worked with paper source documents, which were after transcribed to an electronic data program. With this transcription I could better confirm and verify the consistency of source documents data in paper and the adherence to inclusion/exclusion criteria. I think, if the data collection were directly to an electronic system it would make the work of the team easier, reducing the amount of work dispensed with this task, reducing the steps of data entry, and probably, also could minimize the risk of transcription errors and other errors. To this process work smoothly, the electronic solution must be well designed, tested and validated, responding to the needs of the investigators and the trial (41, 42).

4.2.1.1.6. Work plans

The work plans are used to guide (physicians and nurses) during the clinical trials according the protocol specifications. This task is, essentially, the management of the protocol needs with the staff availability while the team is not large, defining the tasks of each member. These documents are very important and a small mistake can lead to a big deviation of the protocol, and due to this, after the work plans are complete a different person conducts a quality control to assure that the plan is well designed. I had the opportunity to perform both of these tasks, create the work plans according the protocol needs and also perform quality control when the work plans were created by other person.

4.2.1.1.7. Stock control and inventory

When I arrived to Phase I Unit, it was still being equipped so I had the opportunity to participate in that job. Because of my Nursing background I was preferentially allocated to clinical equipment and consumables. During this phase I learned how to contact the suppliers and request budgets, then comparing the offers and present the best choices to the Managing Partners to their approval or disapproval. Searching for these materials also demanded that I was informed about the product characteristics, which improved my knowledge about these materials / equipments.

Nowadays, the unit is equipped but it is still necessary to check the stock and ordering more material and other trial specific products. I have done this task and understand that keep the stock up to date it is very important to ensure the quantities needed and to calculate/control the expenditures.

Globally, this task allowed me to better know the equipment and material that the Unit contains, and also improve my skills regarding how to deal with suppliers.

4.2.2. My experience as a Research Nurse

4.2.2.1. Screening, Admission, Confinement and Follow-up

The Research Nurse in the different moments of the clinical trial depends of the CTP guidance.

Generally, according the CTP, the volunteers must be screened, and this screening procedure includes a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory tests. The clinical laboratory tests will comprise hematology, biochemistry, coagulation, urinalysis, and HIV and hepatitis B and C serology. A urine test to screen for drugs of abuse and a breath ethanol test will be performed at screening. In women a serum beta-hCG pregnancy test will also be performed.

In the admission the volunteers are, usually, screened for abuse of alcohol, drugs and pregnancy test (in case of women) and also have a new medical history update. In case of any change its clinical relevance it is evaluated by the physician and the volunteer can be included or excluded to participate in the clinical trial.

The confinement is the moment where the volunteer is restrained in the hospital. The last clinical trials included periods of confinement because of the blood collection (bioequivalence clinical trials).

It can happen that the clinical trial do not include confinement, it depends of the trial design.

At the end of study the volunteers repeat vital signs measurement, hematology, plasma biochemistry and serum pregnancy test (if woman) tests to verify that they leave the trial as healthy as they were when they were included in the trial.

4.2.2.2. Emergency Cart Development and Maintenance

Blueclinical Phase I has appropriate procedures, equipment, medicines and trained staff to deal with a medical emergency that might arise during a trial.

I had the opportunity to collaborate to the Emergency Cart development and now for its daily maintenance, according the applicable defined procedures.

The emergency equipment and rescue medication is organized and maintained according to a SOP developed with that purpose. The emergency cart has a defibrillator with an ECG monitor; an oxygen cylinder; oropharyngeal airways and face masks; Ambu bag; laryngoscope and endotracheal tubes; consumables such as intravenous cannula and fluid infusion sets; emergency medicines, including intravenous fluids and others.

All these components are verified monthly, in order to verify the adequate conditions and expire dates. The emergency cart is sealed with a lifeline that is verified every working days or every day in case of presence of volunteers in the unit.

At the same time Phase I Unit is on a hospital site and have a written agreement for 24-hour access to the hospital's resuscitation team, to arrive in the unit within a few minutes of an emergency. The resus team can be called calling “222”. Blueclinical clinical team is trained in basic, immediate or advanced life support procedures, respectively, BLS, ILS, ALS as appropriate.

4.2.3. Other Tasks

4.2.3.1. Laboratory

During this time at Blueclinical I also had the opportunity to participate and learn about the laboratory procedures, such as, the activities pre-trial as labelling and quality control, during the trial as pipetting and storing the samples and after trial completion as sample shipment. Laboratory procedures require a maintenance control of the equipment used, for example the pipettes and the centrifuge which also require a periodic calibration to ensure the correct functioning and guarantee a reliable result.

4.2.3.1.1. Labels and Quality Control

The labels contents are previously defined by the protocol or the sponsor, if not, according Blueclinical internal procedure. The label must contain a minimum set of information, such as, protocol no., subject number, study period, sample number, sample series, matrix type. After the labels printing, the entirety of labels are copied and archived in TMF. After the copies are ready, a different person of who did print and copied the labels perform labels' quality control. The quality control aims to verify if the label information is complete and accurate.

In different occasions, I performed both of these tasks according the requirements of Blueclinical procedures, it requires careful attention to avoid errors later in the trial.

4.2.3.1.2. Sample Management

The sample management includes: Supply, preparation, labeling, handling, shipment and storage. All these steps are planned by the laboratory technician in advance and according to protocol or instructions of the bioanalytical laboratory. I had a little or no experience in the laboratory practices, but I understood the high importance of the sample management since the samples are collected till the shipment procedure. The appropriate storage conditions (according to the protocol instructions) must be ensured, and the refrigerators/freezers are continuously monitored by a temperature logger that alerts in case of deviation of the pre specified temperature range. The storage room has access to control restricted to authorized staff. And finally, the last contact with the samples is the shipment procedure, at this moment, the samples are packaged according to the

bioanalytical laboratory instructions and according to International Air Transportation Association (IATA) Dangerous Goods Regulations. I performed an eLearning IATA training learning about the required packaging and documentation practices regarding biological samples and dry ice to better understand this process.

During the all process, there are specific forms to fill, such as the records of sample processing at the very moment when it happens thereby generating accurate data. These records are archived in the TMF.

4.2.3.1.3. Maintenance and Calibration of Laboratory and Clinical Equipment

According the Good Clinical Laboratory Practice (GCLP): "*Equipment used should be periodically inspected, cleaned, maintained, and calibrated, as appropriate. Records of such maintenance and any unscheduled maintenance or calibration should be retained*."(43).

The laboratory equipment has a maintenance plan according to each equipment specifications. For example, the refrigerators and freezers suffer a periodic verification detailed in the operations manual. The refrigerators and freezers have also an uninterrupted power supply and emit an audible alarm or a visual sign in case of malfunctioning. Due to this, these equipment's are also connect in a centralized way to the hospital alarms (43).

It was a learning point because I could understand the need of tracking the conditions in how the equipment's are working in order to both assure the quality of the clinical trial results and also to ensure the safety of the volunteers who are screened and evaluated with this clinical equipment's.

4.2.3.2. Experience report after an inspection

Phase I Unit had a regulatory inspection conducted by INFARMED, which was another learning moment.

Generally, inspections aims to verify (44, 45):

- The integrity of the data submitted;
- Presence of adequate infrastructures;
- Measures implemented to protect subject's interest and safety;
- Quality management system;
- Compliance with the principles of ICH-GCP and applicable legislation.

This action helped me to understand the functioning of an inspection and the preparation for its implementation. It was a valuable learning, because I find myself faced with the inspection for the first time. At the end of the inspection, the findings are discussed and a final report inspection is sent, and the inspected site must implement effective Corrective and Preventive Action Plan (CAPA) to solve the problems found.

I must mention that the contact with the competent authorities was very useful, regarding their valuable presence and their inputs. Their organization in this area allow them to control what is done in clinical research. INFARMED is an orientation point, and regarding their experience they can evaluate what is been done and present suggestions for improvement actions to implement. And, despite being a very demanding action and very time-consuming, it is essential to standardize practices, regulate procedures, ensuring heights of success and the value creation in the context of clinical research.

4.2.3.3. Clinical Study Report – eCTD Module 5

Clinical Study Report (CSR) summarizes the results of each clinical trial involving an investigational product. Its organization aims to contain clinical data and statistical descriptions, presentations, and analyses (46).

I had the opportunity to contribute to the preparation of a CSR, more specifically Module 5, I could help with the document management, preparing documents in pdf format for use in eCTD (Common Technical Document) submissions.

This participation allowed me to better understand the requested document granularity which translates the organization of the CTD. The CSR includes a large quantity of documents, therefore a good document management is a very important key to a successful submission.

5. Discussion

It was with great concern that I grabbed this challenge but at the same time I found it an interesting project immediately. Despite knowing in theory, a little of Phase I trials, in practice, until September last year, I had no experience in the area.

I was appointed as a Clinical Trial Assistant Trainee, and when I was asked to take over this function, I was immediately aware of the importance of this undertaking, however, I felt a little afraid. Blueclinical provided diverse trainings who helped me to improve complementary skills that were useful to perform this function in the Phase I Unit, and I have done some autodidactic work to learn of some aspects that were important to my work, such as, reading national legislation and applicable international guidelines.

I could understand that even if the clinical trial is internationally funded, with an international sponsor, the conduction of the clinical trials implies the involvement of the country directly involved in research, mainly through its competent authorities. I could understand the importance of transparent and efficient communication with the authorities, because this collaboration ensures that the conduction of the clinical trial gathers the requirements in respect of scientific, regulatory and ethical aspects.

This training led me to dwell on the BA/BE trials to understand the principles, methodologies, skills and attitudes necessary to implement in order to improve the quality of services and meet the challenges that appears to clinical research. This allowed me to understand the importance of the role of the CTA, the need to know how to play a role of coordinating logistics and working collaboratively with the team and Blueclinical management board.

There were situations that caused me more constraint due to unexpected changes of timelines. Those situations induced an increase on my stress level because in a split second all the priorities changed and it demands a great capacity of adaptation to new challenges. It was difficult to cope with these changes, especially since I am a novice. One of the strategies I found very important and useful to deal with this, was always to have a “Plan B” and never dismiss the associate risks to each timeline once they can change without previous notice. These were also learning points, since it is very likely that similar situations will happen in the future and at that time I'll be more prepared.

I became aware of the challenges facing clinical research in the current context and the emerging opportunities. It is my belief that the challenges are more difficult to operationalize, but vital to the

present time. I realized the rigor required in clinical research and the need for justification of our practice by collecting evidence. Furthermore, the learning process has been crucial to define improvement actions and how to implement them.

As I, Blueclinical Phase I Unit was taking its first steps, so, it was even more challenging, because I could participate in an early stage of the Unit development activities, such as, SOPs writing, material acquisitions and other activities. This allowed me to learn some hurdles in project management, such as budget and timelines definition and fulfillment. Taking these “baby-steps” was crucial to my learning outcomes during this training period. Now, both I and the Unit benefit from all the evolution and growth. As I proposed in the beginning of this training, these tasks helped me to achieve the goal: “be proactive and help to brainstorm new ideas” to improve the functional network of the Unit.

The final balance is very positive. I believe that most of the objectives were met and I am now much more able to apply this knowledge in future tasks. Nevertheless, I think I still have to continue to improve my skills in project management, as I want to perform these tasks in the future, working closely with investigators, project managers and other study team members to ensure optimal coordination of clinical research activities.

6. Conclusion

During this period of time I actively participated in several clinical trials. I noticed a significant personal evolution and professional development in this area and I could also verify that a practice-based experience allows an effective learning.

BA/BE clinical trials are complex and a highly competitive market and to survive and to be successful it is required an extensive knowledge about the process, regulations and project management. Furthermore, experience is also required, so I am very glad for have had this opportunity at Blueclinical, because this training contributed for both: first, to increase my knowledge and second, to acquire some experience.

One of the aspects I noticed an improvement on was my organizational and time management skills. During the first months I felt the need to improve this aspect in order to better organize my time and, ten months later I can say I accomplished it, by acquiring simple but sacred strategies, such as, writing task lists and defining priorities. Furthermore, now I can better assess some of the major difficulties that can arise during the preparation and development of Phase I clinical trials and I developed strategies to deal with it. Some difficulties were, for example, time stress, reworking the procedures and training the clinical team to be compliant with the protocol and SOPs. The strategies included better organization and a supportive teamwork environment.

I had also learned that communication is an essential tool for this job, in many respects, including communication with competent authorities, clients, volunteers, and even within the team. I was able to improve it by performing some activities during my internship, for example, by recruiting volunteers. Although I learned a lot already, in the future, I still would like to better develop my communication skills, to efficiently communicate with sponsors and study teams.

As I mentioned before, organization, time and resources management are essential to the success of any project, as well as teamwork and motivation and these were my pillars. My goals to the future include to growing within the clinical research, improve my leadership, possibly, by attending a leadership course, interpersonal and technical skills and assume additional responsibilities. And, last but not least, continue to learn and increase my value to high quality clinical research.

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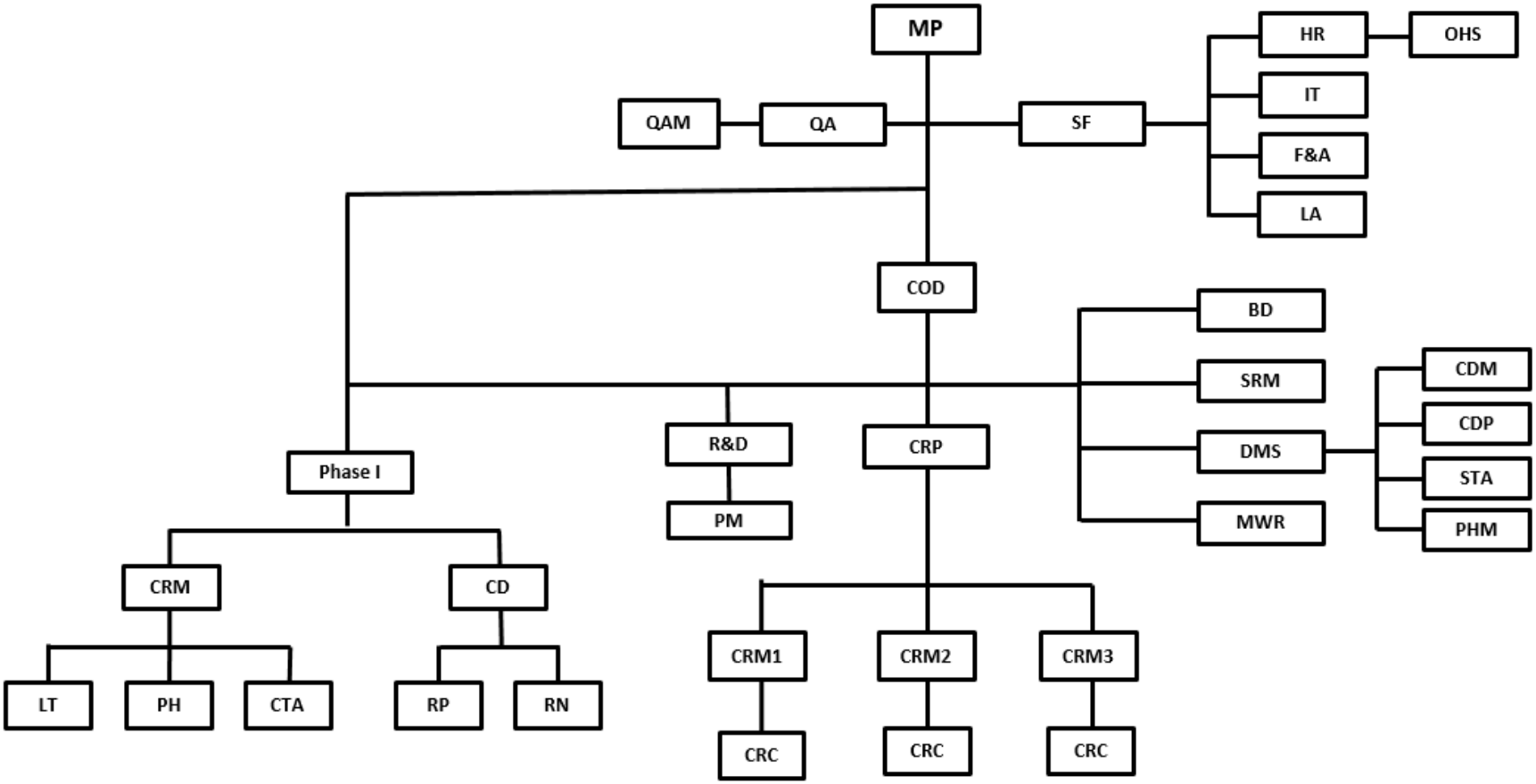
Appendix A – Blueclinical Organogram and List of Acronyms



List of Acronyms:

BD – Business Development

CD – Clinical Director

CDM – Clinical Data Management

CDP – Clinical Data Programming

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

LA – Legal Affairs

LT – Laboratory Technicians

MP – Managing Partners

MWR – Medical Writing and Reporting

OHS – Occupational Health and Safety

PH – Research Pharmacy

PHM – Pharmacometrics

PM – Project Management

QAM – Quality Assurance Manager

R&D – Research and Development

RN – Research Nurses

RP – Research Physicians

SF – Support Functions

SRM – Safety Risk Management

STA – Statistics