Universidade de Aveiro Secção Autónoma das Ciências da Saúde

2011

Cátia Sofia Teixeira Magalhães

Relatório de Estágio em Monitorização de Ensaios Clínicos

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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 do Doutor José Aleixo Dias, Director Médico dos Laboratórios Pfizer, Lda. e do Professor Doutor José Carlos Fontes da Neves Lopes, Professor Auxiliar do departamento de Física da Universidade de Aveiro.

Dedico este relatório aos meus pais e irmãs por serem a minha fonte de motivação.

o júri

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agradecimentos

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Ao Diogo por ser um pilar na minha vida e por toda a compreensão ao longo destes anos.

palavras-chave Pfizer, Estágio, Ensaios Clínicos, Country Clinical Operations, Monitorização.

resumo

Este relatório descreve a minha experiência de 9 meses enquanto estagiária nos Laboratórios Pfizer, Lda.,uma das indústrias farmacêutica mais especializada em pesquisa biomédica.

Este estágio decorreu em dois formatos: formação multidisciplinar e monodisciplinar.

A formação multidisciplinar teve como objectivo obter uma perspectiva mais alargada das diferentes unidades de uma indústria farmacêutica, envolvendo deste modo a participação em diferentes unidades desta empresa.

A formação monodisciplinar concentrou-se na área de monitorização de ensaios clínicos, decorrendo na unidade de ensaios clínicos – *Country Clinical Operations* – com o objectivo de adquirir experiência e competências na condução de ensaios clínicos.

O estágio multidisciplinar permitiu-me adquirir competências em diferentes unidades da companhia e perceber qual a sua função dentro da companhia.

O estágio monodisciplinar permitiu-me compreender com maior profundidade o papel do monitor na condução de ensaios clínicos e o quão importante é para garantir a segurança, direitos e bem-estar dos participantes nos ensaios clínicos e garantir a integridade dos dados recolhidos. Permitiu me também contactar com locais de ensaio e perceber quais os desafios que temos de ultrapassar para voltarmos a ser um país de interesse para a condução de ensaios clínicos.

keywords Pfizer, Internship, Clinical Trials, Country Clinical Operations, Monitoring.

abstract

This report describes my 9-month experience as an intern at Laboratórios Pfizer,Lda., one of the most specialized companies of biomedical research in the world.

This internship took place in two formats: multidisciplinary and monodosciplinary training.

Multidisciplinary training had the objective of obtaining a broad perspective of the different units of the company involving the participation in these different units.

The Monodisciplinary training carried out in the Clinical Country Operations unit was focused in monitoring clinical trials. The objective was to obtain experience and skills in the conduction of clinical trials.

Multidisciplinary internship allowed me acquire skills in each unit where I spent time and realize what are the functions of each unit in the company.

Monodisciplinary internship allowed me to deeply understand the monitor's responsibilities in conducting clinical trials, and how important is to ensure the rights, safety and welfare of subjects participating in clinical trials and assure the quality, reliability and integrity of data collected. It also allowed me to contact with study sites and understand what are the challenges that we need to overcome and become again an eligible country to conduct clinical trials.

Table of contents

Tables and Figures

Abbreviations

CCO	Country Clinical Operations
CEIC	Centralized Ethics Commission for Clinical Research
CFR	Code of Federal Regulations
CNPD	National Committee for Data Protection
CRF	Case Report Form
CTA	Clinical Trial Application
GCP	Good Clinical Practices
EU	European Union
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INFARMED	National Authority of Medicines and Health Products
MA	Marketing Authorization
PTA	Pre Trial Assessment
QC	Quality Check
R&D	Research and Development
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
USA	United States of America

Introduction

From September 2010 through May 2011, I developed my internship within the scope of the Master's degree in Pharmaceutical Biomedicine, which took place at Laboratórios Pfizer, Lda., a leading pharmaceutical company.

I established the following main objectives to be achieved during the internship:

- To gather basic knowledge in various areas, to be involved with activities from the different units, in order to understand the multidisciplinary framework of this company;
- To understand in depth the conduction of clinical trials, working mostly within the Country Clinical Operations (CCO);
- Acquire skills and experience in the conduction of clinical trials;
- Establish networking with peers, hierarchical levels, institutions, researchers and other health professionals;
- Personal and professional development.

The internship was planned according to the information presented in Table 1. In January I decided the area where I would like to specialize, I chose Country Clinical Operations.

Table 1 – Plan of internship

Unit	Period
Country Clinical Operations	September 1st - 10th
Regulatory Affairs	September 13th - 24th
Drug Safety	September 27th - October 8th
Quality of Procedures	October 11th - 22nd
Quality of Products	October 25th - November 5th
Medical Information	November 8th - 19th
Market Access	November 22nd - December 3rd
Medical Affairs	December 6th - 31st

This internship report describes my working experience during the last 9 months, since September 2010 to May 2011, describing Pfizer and defining its role inside the clinical research environment, as well as, reporting all activities performed and lessons learned from such activities.

For this purpose, this document is divided in 4 chapters, defined as follows:

- Overview of the host company and clinical trials: this chapter describes Pfizer, defining where it fits in the clinical research framework, its purpose, organization and work developed. The state of the art of clinical trials is also described in this chapter;
- Multidisciplinary internship: this chapter reports the activities developed in all medical related units of Laboratórios Pfizer, Lda, to understand the objectives and comprehend the type of work performed in each of these units, as well as how they fit in the company framework;
- Monodisciplinary internship within the Country Clinical Operations unit: this chapter describes the role of a monitor in the conduct of clinical trials and the activities in which I have participated;
- Discussion: this chapter gives an overview of my internship experience, discussing what I learned during this period and the acquired competences.
- Conclusions: in this chapter I present the conclusions about my internship.

1. Overview of the host company and clinical trials

This chapter describes the host company, its purpose, activities and its structure and an overview of clinical trials.

1.1. Overview of the host company

My internship took place at Laboratórios Pfizer, Lda., in Lisbon. Pfizer is one of the major and most specialized companies of biomedical research in the World, resulting from the acquisition of others pharmaceutical companies that have a huge worldwide growth. The objective of Pfizer is to make available safe, effective and affordable drugs and related health care services to the people who need them(1).

Pfizer was funded by the cousins Charles Pfizer and Charles Erhart in 1849, and has been in Portugal for more than 50 years(2). This pharmaceutical company provides a huge portfolio of products and drugs in support wellness and prevention, as well as for treatment of diseases across a broad range of therapeutic areas. In the research and development area, Pfizer has an industry-leading pipeline of promising new products in a variety of therapeutic areas, of which I highlight Alzheimer's disease and cancer (1). Another objective of Pfizer is to ensure through partnerships with several organizations, that people everywhere have access to treatments and quality health care (1).

Pfizer is present in 180 countries, with its headquarters in New York, and has research centers in United States of America (USA), Europe and Japan, as well as, some pilot centers around the World, and factories in 33 countries (1).

1.1.1. Pfizer History

Pfizer was founded in 1849. From the start, this pharmaceutical company has remained dedicated to discovering and developing new and better ways to prevent and, to treat disease and improve the health and quality of life for people around the world. Since 1849, Pfizer grew and expanded to the whole World, acquired other companies and products, increased the investment in drug development and became more social responsible. At this level, worthwhile mentioning the growth of patient assistance programs, to better respond to the World’s diverse health needs. Along the years, the structure and managerial process of the company suffered several changes, turning in what can be seen today. The Table 2 describes in summary some of Pfizer’s milestones.

Table 2 – Brief timeline about Pfizer's history

1849 – 1950	Cousins Charles Pfizer and Charles Erhart open Charles Pfizer & Company. First product is a palatable form of santonin. Launch of the first domestic production of tartaric acid and cream of tartar, products vital to the food and chemical industries. Pfizer marks its 50th anniversary. Its portfolio includes a wide array of industrial and pharmacological products, anchored by citric acid, camphor, cream of tartar, borax, and iodine. Alexander Fleming discovers the antibiotic properties of the penicillin mould, an event destined to make medical history and to change the course of Pfizer's future. Pfizer starts large-scale production of penicillin. Pfizer becomes the world's leading producer of vitamin C. Pfizer starts the production of vitamin B-2, or riboflavin, and eventually develops a vitamin mix that includes riboflavin, thiamin, niacin, and iron. Terramycin® (oxytetracycline) - is the result of the Company's first discovery program.
1952 – 1989	Pfizer establishes an agricultural division dedicated to offering cutting-edge solutions to animal health problems. Pfizer introduces: Vibramycin® (doxycycline hyclate), Minipress® (prazosin HCI), Feldene® (piroxicam), Glucotrol® (glipizide), Unasyn® (ampicillin sulbactam), Procardia® XL (nifedipine). Pfizer acquires Mack Illertissen, a prosperous manufacturer of pharmaceutical, chemical, and consumer products. Pfizer also leads the ongoing worldwide battle for intellectual property protection to encourage and safeguard innovation.
1990 – 1999	Pfizer launches: Diflucan® (fluconazole), Zoloft® (sertraline hydrochloride), Norvasc® (amlodipine besylate), and Zithromax® (azithromycin), Cardura® and Viagra®. The Animal Health Division purchases SmithKline Beecham's animal health business. Fortune® magazine names Pfizer the world's most admired pharmaceutical company. Pfizer continues its reign as most admired in 1998. Pfizer invests more than $3.3 billion in research and development.

2001 - 2010	Pfizer launches Zeldox® (ziprasidone hydrochloride), Relpax® (eletriptan HBr) Caduet® (amlodipine besylate and atorvastatin calcium), Lyrica® (pregabalin), Ecalta™ (anidulafungin), Champix™ (varenicline), Sutent® (sunitinib malate), Celsentri™ (maraviroc) and Toviaz (fesoterodine), Vfend® (voriconazole). On 2003 Pfizer Inc and Pharmacia Corporation combine operations. Pfizer Inc. is selected by Dow Jones and Co. to be included in the Dow Jones Industrial Average, which is the best-known stock market barometer in the world. Pfizer announces the launch of *Mobilize Against Malaria.* Customer-focused business units allow Pfizer to better anticipate and respond to customers' and patients' needs, and to respond to changes in the marketplace. Pfizer launches a new Medicine Safety Website to help healthcare professionals and patients make better informed decisions about treatment options. Pfizer launches its Global Regenerative Medicine Unit. Pfizer acquires Wyeth, creating a company with a broad range of products and therapies. Pfizer announces a diversified research and development (R&D) platform named – Pfizer Worldwide Research and Development. Pfizer acquires King Pharmaceuticals Inc.

Source: Pfizer Website (1)

1.1.2. Pfizer Leadership and Structure

Pfizer's Executive Leadership Team is composed by the leaders responsible for financial, strategic and operational decisions for the company (1).

At the level of research and development two distinct research organizations were created to maximize new opportunities in biomedical research and bring drugs to patients more quickly. The *PharmaTherapeutics Research & Development Group*, which focuses on the discovery of small molecules and related modalities; and *The Bio Therapeutics Research & Development Group*, which focuses on large-molecules research, including vaccines (1). Pfizer has also developed an enhanced commercial operating structure through the creation of health care businesses – *Primary Care, Specialty Care, Oncology, Emerging Markets, Established Products, Consumer Healthcare, Nutrition, Animal Health and Capsugel.* This structure, allows Pfizer to have a strategic vision of the market and to quickly take advantage of opportunities to advance its business by increasing support for successful development and delivery of new drugs, establishing partnerships with key stakeholders, entering into co-promotion and licensing agreements with other pharmaceutical industries, investing in new technologies and acquiring new products and services from outside the company (1).

In Portugal, there is the same health care business organized on the following structure: Worldwide Biopharmaceutical Businesses, Diversified Businesses and Supporting Functions. In the Worldwide Biopharmaceutical Businesses, Portugal has four business units – *Primary Care, Oncology, Established Products, Specialty Care*, three business units in Diversified Business – *Consumer, Nutrition and Animal Health*, and several units in Supporting Functions. Supporting functions are transversal to all business units, and they are: *Access & Public Affairs, Business Technology, Procurement, Human Resources, Country Clinical Operations, Legal, Safety, Medical Information, Distribution, Finance and Manufacturing*.

1.2. Overview of clinical trials

The first clinical trials were not exactly randomized, double-blinded, placebo-controlled clinical trial. But the modest experiments may have been one of the first times in human history that a medical test, although rudimentary, guided a decision about public health (3). With the time, scientific progression and ethical concerns, the clinical trials became what they are in our days – with a control group, and with ways to eliminate the bias, such as blinding and randomization. The scientific progression was accompanied with a regulatory evolution. The Nuremberg Code (1947) was the only guidance document specifying standards for the review and conduct of human research during years. In 1960, a tragedy happened with a drug called thalidomide. This tragedy was the trigger for pharmaceutical companies and regulatory authorities of different countries to work in legislation that would regulate the evaluation of drugs before they were allowed on the market(4). In 1964, the Declaration of Helsinki was adopted by the World Medical Association in response to the findings of Nuremberg trials. Declaration sets out comprehensive ethical standards for the

conduct of human research and had a significant impact influencing national laws, regulations and guidelines. These laws, guidelines and regulations were implemented to evaluate the safety, quality and efficacy of new medical products in worldwide, in the sixties and seventies (4). In this period the pharmaceutical companies experienced a huge growth, becoming more international and seeking new markets. With different legislation within each country, but with the same purpose industry faced a problem: the need to do in duplicate the same work (4). Other problems like the over rising costs of health care, increased costs of R&D and the need to have safe and efficacious new treatments rapidly available created the need to harmonize legislation (4). This way, in 1990 the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) was created and developed several documents, like quality, safety, efficacy and multidisciplinary guidelines with the aim to give answers to the problems that the industry was facing. Among, these guidelines developed one holds special interest for the clinical trials monitoring: ICH - Good Clinical Practices (GCP) (4). As stated in that guideline, GCP "is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with that standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible" (5).

Today, new drugs need to prove to be safe and effective before being authorized to market. It is through clinical trials that those parameters are evaluated. All clinical trials need to have scientific purpose – a rationale – and should be conducted according to scientific principles and ethical issues, in order to achieve the clinical trial objectives (6).

1.2.1. Clinical trials classification

Clinical trial is defined as stated in ICH GCP as "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy." (5).

The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified according to when the study occurs during clinical development and four phases are considered:

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its tolerability, safety, determine a safe dosage range, and identify side effects. This phase is carried out in

healthy people; however in certain diseases, like cancer, this phase is carried out in people with the disease being studied (7).

Phase II: In this phase the drug or treatment is given to a larger group of people (with the study disease) with the objective to explore therapeutic efficacy in patients and short-term side effects and identify common risks for a specific population and diseases (7).

Phase III: This phase is carried out in large group of people. The primary objective is to confirm or demonstrate the therapeutic benefit of study drug (7). In addition, to the confirmation of efficacy, this phase is useful to monitor side effects, compare the drug with standard treatments, and collect more information that will allow its safe use (7).

Phase IV: These studies are carried out after the marketing authorization of the drug or treatment, and the principal objective is the collection of efficacy and safety information associated with long term use of the intervention. They are not needed to obtain the approval from authorities. However, they are important for optimizing the use of drug or treatment (7).

Clinical drug development is often associated to four temporal phases. However, a classification per objectives is preferable, once one type of trial may occur in several phases and emerging data will frequently prompt a modification of the development strategy (7). For example, human pharmacology studies can occur during all development phases of a clinical trial, as it is presented in the
Figure 1. This figure shows the correlation between development phases and type of studies. (7). As presented in Guideline E8 – General Considerations For Clinical Trials, clinical trials can be classified according to study objective in: Human Pharmacology, Therapeutic Exploratory, Therapeutic Confirmatory and Therapeutic Use (7).

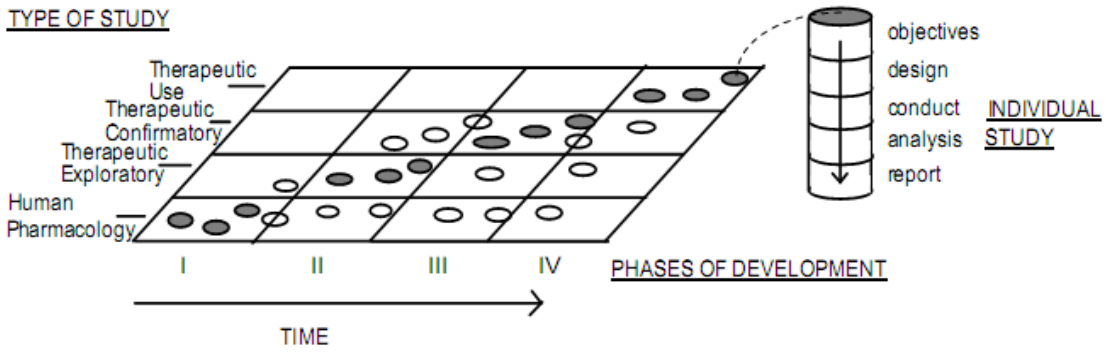

Figure 1 – Correlation between development phases and types of study. Reprinted from ICH E8 (7).The gray circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual.

1.2.2. Clinical trials regulation

A clinical trial is a highly regulated activity due to its sensitivity relatively to ethical and regulatory issues. As stated above, ICH GCP is an international standard for the conduct and reporting of clinical trials. However, countries have specific regulations that govern the conduct of clinical trials and these must also be applied. In addition to ICH GCP and regulations of the country in which the trial is being conducted, trials may also be subject to the US Code Federal Regulations (CFR) and/or European Union (EU) Clinical Trials Directive, depending on where the trial is being conducted and where the data will be submitted. For example, trials in Europe that will form part of an investigational new drug application will need to be conducted in accordance with US CFR. In most cases, the additional regulations simply provide further detail that is found in ICH GCP. However it is important be compliant with all regulation.

In the USA it is the Code of Federal Regulations that regulates clinical trials, specially the title 21 (21 CFR) that have the rules generated by the Food and Drug Administration. 21 CFR also regulates trials that are conducted outside of USA as part of an investigational new drug (8).

In Europe the clinical trial directive – 2001/20/EC – provide a legal framework for the application of GCP to all trials conducted in member states of the EU. This directive was transposed into national law in each member state of the EU (9). In 2005, another directive enter in force, 2005/28/EC, establishing principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use (10).

In Portugal, the following rules must be followed:

<u>European Commission Directives:</u>

- 2001/20/EC
- 2005/28/EC

<u>National Law:</u>

- Law no 46/2004: transposition of Directive 2001/20/CE (11);
- Decree-Law no 102/2007: transposition of Directive 2005/28/CE (12);
- Law no 67/98: protection of personal data (13).

<u>Other essential Documents:</u>

- Declaration of Helsinki (2008 version): definition of ethical principles for medical research involving human subjects (14).

To conduct clinical trials in Portugal they need to be previously approved or obtain a favorable opinion by:

- Commission of Ethics for Clinical Research (CEIC) (11);
- National Authority of Medicines and Health Products (INFARMED) (11);
- National Committee for Data Protection (CNPD) (15).

1.2.3. Monitor role

The monitor is responsible for ensuring that the trial "is conducted, recorded and reported in accordance with the study protocol, Standard Operating Procedures (SOPs) and all the applicable ethical and regulatory requirements defined above", as stated in ICH-GCP (5).

This visits carried out by the monitor at the study sites have the purpose, as stated in ICH GCP (5), verify:

- The rights and well-being of human subjects are protected;
- The reported trial data are accurate, complete, and verifiable from source documents;
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

It is supposed that the monitor(s) act in accordance with the sponsor requirements to ensure that the trial is conducted and documented properly, by carrying out the following activities when relevant and necessary to the trial and the trial site (5):

- Be the main line of communication between the sponsor and the investigator;
- Verify if the investigator has adequate qualifications and resources (facilities and human resources) and remain adequate throughout the trial period;
- Verify, for the investigational drug(s):
    - The conditions of local (locked cabinet, temperature...), the storage times, if the supplies are enough throughout the trial;
    - If only eligible subjects are receiving investigational drug and in the corrects doses;
    - If staff know how to manage the investigational drug - use, handle, store, and return;
    - If there is a proof of the following activities and if they were controlled: reception, use, and return of the investigational drug;
    - If unused investigational drugs are in compliance with applicable legislation and sponsor requirements;
- Verify if the investigator is in compliance with the approved protocol and all approved amendment(s), if any;
- Verify if all written informed consents were obtained from the subjects before any trial procedure;
- Ensure that all essential documents and trial supplies needed to conduct the trial were received for the investigator, and are in compliance with the applicable regulatory requirement(s);
- Ensure that the investigator and the investigator's trial staff are adequately informed about the trial and trained;
- Verify if all investigator's trial staff are performing the delegated trial functions, and if they are training or knowledge to have some duties;
- Verify the eligibility of enrolled subjects;
- Report the rate of subjects recruited even the screening failure must be reported;

- Ensure the source data verification, if the source documents and other trial records are accurate, complete, kept up-to-date and maintained;
- Verify if documents provided by the investigator, like reports and submissions, are complete, accurate, legible, dated, identify the trial and if they are provided in the due time, according to applicable legislation and sponsor requirements;
- Verify the data entered in CRF with source documents and other trial-related records in order to ensure the quality of data collected:
    - All data required by the protocol are reported accurately on the CRFs and in accordance with the source documents;
    - All therapy and its modifications are well documented for each subject.
    - Past history, adverse events and concomitant medications are reported as required by protocol on the CRFs;
    - Any visit or protocol procedure not performed is clearly reported on CRF, and when applicable documented the protocol deviation;
- Verify if there is a report and explanation of all withdrawals and dropouts of enrolled subjects from the trial on the CRFs;
- Verify if there is any CRF entry error, omission, or illegibility is found, the monitor must inform the investigator to correct adequately. Corrections made need to be dated, explained and initialized by trial staff with this duty delegated;
- Verify if all adverse events, specially serious adverse events are reported in the due time periods required by GCP, the protocol, the ethics committee, the sponsor, and the applicable regulatory requirement(s);
- Verify if the investigator is maintaining the essential documents;
- Ensure that all deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements are communicated to the investigator and appropriate action designed is implemented to prevent recurrence of the detected deviations**.**

1.3. State of the art of clinical trials

The whole world is facing an economic crisis. The pharmaceutical industry is not an exception and is has also been affected. The development of successful novel drugs is decreasing in spite of the continuous rising investment in pharmaceutical research and development (16). The year of 2004 represented a 20-year decrease in introductions of new chemical entities Worldwide (17). However, the costs associated per successful new chemical entity have risen to an estimated $800 million or more (16). A high rate of clinical failure, estimated to be of 70% – 90% of candidates, is the principal responsible for this costs (18). About 50% of compounds tested in phase 3 trials are a clinical failure, which represents a concern of a high investment that will not be returned (19).

An investment in more innovative approaches and in small markets (rare diseases) may be discouraged by the high cost associated of successful drug development. Additionally; the industries have a period of exclusivity before the launch of generics that cannot be enough to obtain the return. So, during this period some companies need to use "aggressive marketing techniques" (19).

Nowadays, the pharmaceutical companies are experiencing difficulties in maintaining the innovation of other times. At the same time, the societal demands have been growing about the certainty of outcomes of drug therapy. This trend raises significant concerns, since there are several conditions that have not a therapeutic answer or it is unsatisfactory (16). Trends in clinical trials globally will be highly affected in the coming years, as we can see in the Table 3.

Table 3 – Change drivers in clinical trials

Change drivers	
Pressure on Pharma R&D spend	• R&D expediture is directly linked to the budget allocated to clinical trials. • R&D costs exhibited continuous, long-term growth. However, as from 2004 R&D productivity declined.
Increase disease prevalence	• Epidemiologic studies may indicate therapeutic areas where demand for drugs, and thus clinical trials, will increase.
Blockbuster patent expiry Will reduce clinical trials Spending	• Several patents will expire; pharmaceutical companies will be exposed to revenue declines as a result of patent expiring. This can have an impact on the launch of new products.
Patient empowerment will increase	• Patients and patient groups will have more participation and influence on recruiting, protocol and information sharing through a networked community. However the ethical concerns and pressures will continue to increase.
Treatment personalization &Pay for performance	• The practice of personalized medicine will require specific clinical trial design. • Life licensing: cumulative testing and release of the drug throughout its lifecycle. • Outcome-focused clinical trial designs.

Source: PwC, 2011 (20)

With the purpose to fight this crisis a set of policies have been implemented through initiatives such as Innovative Medicines Initiative (IMI) in Europe and Critical Path Initiative (CPI) in the USA that has the objective to build a more collaborative system for pharmaceutical R&D and to accelerate the development of more effective and safe drugs for patients (16, 21).

Randomized clinical trials have been the mainstream of pharmaceutical product development for decades, but they need to be designed and carried out in a different way in the future, to sustain the drug development. Interactive technologies, interaction between companies and academies, development and validation of biomarkers, adaptive designs and new ways to recruit and monitor patients need to be developed and implemented (22). Clinical research needs a revolution to be able to return to the old times and develop successful drugs.

One issue that arose in the last years is the decrease of clinical trials conducted in the EU and USA and its increase in other countries, like Asian countries, and European Eastern countries. Emerging markets are characterized for having access to large patient populations to run the trials. This is one reason why these countries are attracting a growing number of large-scale clinical trials. Another advantage of these countries is the lower costs associated of running clinical trials, comparing to EU and USA, and this is the explanation

of the drop in clinical research in EU and USA (20). Existence of improved guidelines and simplified procedures from authorities in emerging markets are other reason. When the pharmaceutical companies facing good established networks that allow the quick approval of clinical trial versus a complex and too long approval process; the preference goes to those that offer better conditions and where companies know that will obtain the return of investment (23).

Another point that has gained presence in clinical research over the last years is the outsourcing of clinical development as a whole or in parts. This has become an important strategic issue for pharmaceuticals that have in the Clinical Research Organization (CRO) the opportunity to save costs, since CRO presents competitive prices, and obtain services with high quality. The services outsourced can include the entire drug development process, or only few phases of the program. With this strategy the industries reduce the time to launch the product in the market, and expenditure on new drug development (24). Outsourcing strategies can vary from the requirements of the sponsor and CRO. However in the last years outsourcing of drug development has gained more acceptance (24).

1.4. Clinical trials in Portugal

The clinical trials setting in Portugal is facing some challenges, as probably many other countries. Regulatory demands have been increasing, there is a decrease of innovative drugs, other countries offer better conditions to run clinical trials and clinical trials are getting more complicated and demand more resources. With these facts, it is expected a decrease in the number of clinical trials performed in Portugal.

The Portuguese regulatory authority – INFARMED has available data from the last years, **Figure 2**, that show the decline of clinical trial application (CTA) submitted since 2006 to 2010 (25). In spite of the R&D crisis, one possible reason for this decrease is the fact that the sponsors choose others countries to carry out the clinical trials.

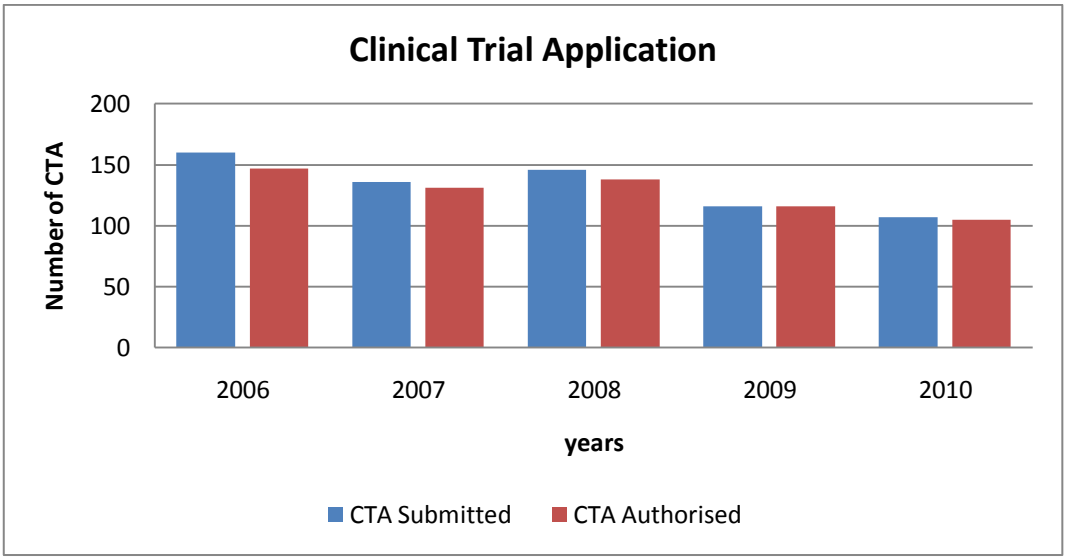

Figure 2 – Number of Clinical Trial Applications done between 2006 and 2010.
Source: INFARMED, 2011 (25)

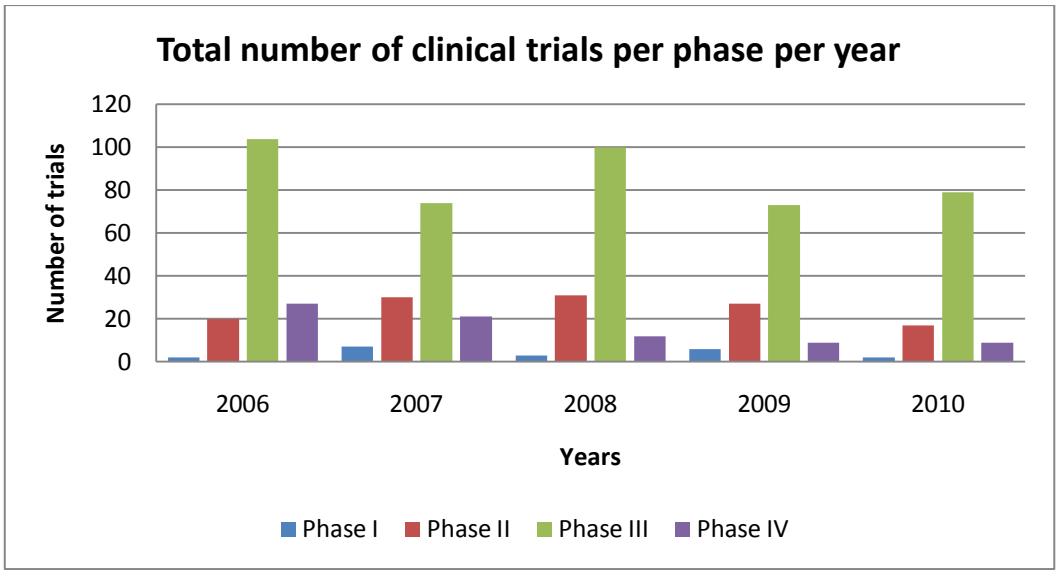

Figure 3 – Total Number of Clinical Trials per Phase per Year.
Source: INFARMED, 2011 (25)

As we can see in **Figure 3**, in Portugal, early phase trials have a small representation, while phase III represents the major percentage of trials performed. Phase IV have decreased in the last four years. In general, all phases suffered reductions since 2006 to 2010. Although the total number of clinical trials is decreasing, the total number of amendments is increasing, as we can see in **Figure 4**.

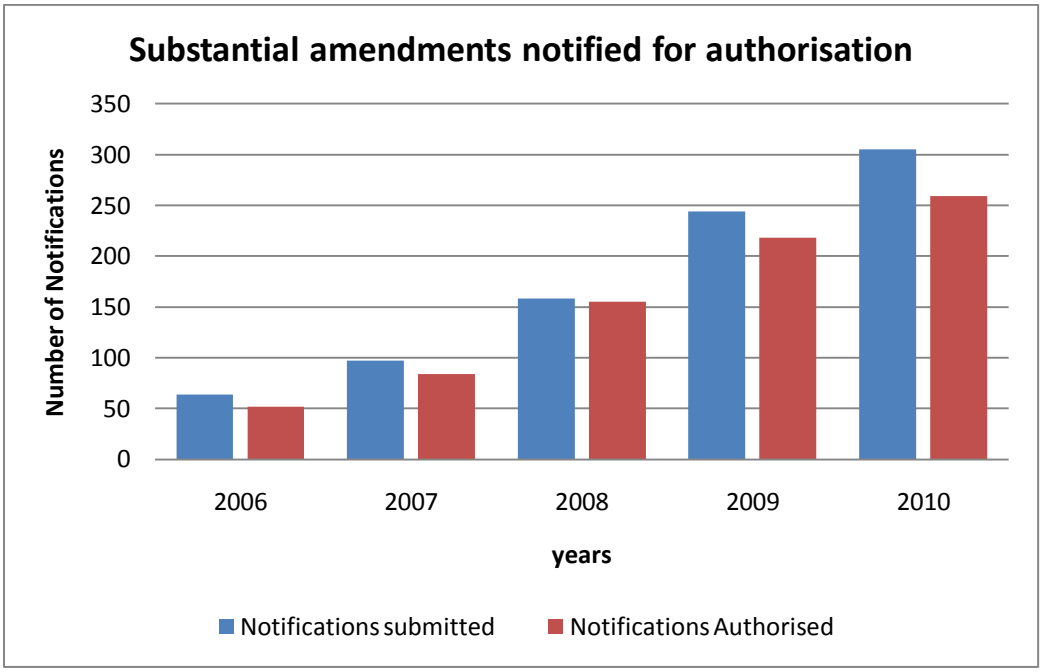

Figure 4 – Number of substantial amendments notified for authorization
Source: INFARMED, 2011 (25)

Portugal has a big problem: the majority of clinical trials performed in Portugal are funded by Sponsors (pharmaceutical companies) and there are very few from academic initiatives, as it is presented in Table 4. This means that most R&D developed in academic context is not always "translated" into clinical research.

Table 4 – Clinical Trials funding- number of clinical trials carried out per sponsor.

Year / Sponsor	2006	2007	2008	2009	2010
Pharmaceutical Company	145	127	139	103	101
Academic institution	8	5	7	12	6

Source: INFARMED, 2011 (25)

During these years there was no significant shift in the spread of clinical trials over the different therapeutic areas. Antineoplastic and immunomodulating, anti-infective and drugs for the nervous system represent the three areas where Portugal carries out more clinical trials as show Table 5.

Table 5 – Number of Clinical Trials per therapeutic area between 2006 and 2010.

Years / ***Therapeutic area***	**2006**	**2007**	**2008**	**2009**	**2010**
Antineoplastic and immunomodulating	49	36	43	36	41
Anti-infective	10	14	19	7	10
Nervous System	20	14	25	24	11
Cardio Vascular	11	10	9	12	11
Sensory organs	13	4	10	7	5
Blood and blood forming organs	17	9	12	6	4
Endocrine System	8	7	1	3	6
Genito urinary	2	6	6	5	4
Respiratory	11	4	3	2	5
Alimentary tract and metabolism	4	3	13	5	8
Musculo-skeletal	5	3	4	5	2
Dermatologicals	3	2	0	3	0
Various	0	1	1	0	0
Total (nº trials submitted and authorized)	**153**	**113**	**146**	**115**	**107**

Source: INFARMED, 2011 (25)

2. Multidisciplinary internship

In this chapter I describe the units where I spent time in multidisciplinary internship, as well as the activities performed in each one.

One of the objectives of my internship was to acquire multidisciplinary knowledge and experience through the training in each unit. The purpose of these activities was to get a broad perspective of what happens in each unit, how they contribute for the Pfizer objectives and how different units interact within the company.

The initial strategy suffered some alterations and because of the lack of human resources in CCO, I started working earlier in this unit.

I participated in various activities, during my internship. Some were mandatory; others were performed only within the scope of this internship. I performed several activities within the following units that will be discussed in depth, separately:

- Regulatory Affairs
- Drug Safety Unit
- Quality of Products
- Medical Information
- Market Access
- Medical Affairs – Primary Care business unit

All these units, except the Primary Care business unit, are Supporting Functions units transversal to all business units in Pfizer.

Before executing any task within these units, the reading of applicable SOPs, legislation and sometimes some journal articles was essential, in order to have a minimal training and be aware of some tasks that I would perform. The time that I spent in each unit was managed by the head of each unit, who established a program of tasks and presentations that would be enough for me to be aware of all the work performed in each unit. Time management, good work structure and people available to demonstrate it knowledge and skills were essential to transmit what a unit does in a short period of time.

2.1. Mandatory actions

At the beginning of my internship, I had a welcome session, where I was taught about the Pfizer's history and structure, as well as procedures about the functioning of the building. I also attended an internal pharmacovigilance training session, mandatory for all collaborators, on how to properly handle safety information. Aspects addressed included definition of safety information, handling of relevant safety information and procedures to adequately report this information to the drug safety unit.

2.2. Regulatory Affairs unit

Regulatory Affairs carries out functions of business support, across the entire lifecycle of drugs: research and development, product registration, launching and marketing authorization (MA). The maintenance of MA involves updating the quality, safety and efficacy information in accordance with current scientific knowledge in order to ensure compliance between what is approved by regulatory authorities and what is manufactured and marketed (2).

The activities developed in this unit had the purpose to give me an idea about what is done there. I started with a presentation about the unit and what are the functions and responsibilities of this unit. To be aware of applicable legislation the reading, prior to start any activity of Notice to Applicants Volume 2 (25) and Portuguese legislation – Decree-Law no 176/2006, 30 August (26) and clarification of some questions with different elements were crucial. The first activity developed was the simulation of the submission of CTA to authorities and submission of amendments. Another procedure discussed was the marketing authorization process. All procedures were discussed in detail – national procedure, mutual recognition procedure; centralized procedure and decentralized procedure. I had the opportunity to follow a centralized procedure during my internship in this unit. One important challenge in this kind of submission is the timelines established that need to be met. A related activity with the MA is the submission of alterations. Updated information is sent to authorities to maintain the product authorized and all information available to authorities updated. A package with all information is prepared to notify the authorities. I had the opportunity to prepare this package with the supervision of a regulatory officer. The activity most often performed was the revision of labels and artworks using a specialized tool. It concerns the revision of carton information versus the information that needs to be present and the revision of dimensions of the carton. Another activity often performed was the revision of a summary of product characteristics (SmPC) and package leaflet in accordance with the information presented in English version. I also performed a search with a regulatory officer with the purpose to find possible patent violations to Pfizer products through a search in the web page of INFARMED, of products that obtain authorization from the INFARMED during the patent period of Pfizer products. This way it is possible to monitor the regulatory evolution of major competitors and to anticipate emerging challenges. By curiosity I read the regulation applicable to nutritional products (27-29). I also attended also a presentation about the quality in this unit that is achieved through the following tools: audits, change controls, contact report and metrics.

The partnerships, acquisition of new companies or products, co-licensing were some subjects discussed to show me how it is possible take benefit from the law and how this unit contributes to the growth of company.

2.3. Drug Safety unit

This unit has a great knowledge of the safety profile of products, to properly assess their benefit-risk and avoid harming the health of those who use them daily. The responsibility of this unit is the management of adverse events and notification of any adverse event to regulatory authorities (2).

First of all I attended a presentation about this unit and discussed its responsibilities and functions. All applicable SOPs for this unit were read as also the following regulatory documents: Decree Law no 176/2006, 30 August and Law no 46/2004, 19 August. To manage the tool used to do the report of adverse reactions a specific training is needed. Since I cannot manage this tool, I followed all the procedure of data entry and peer review of data, in order to have a case validated. Doing the follow up of adverse reactions with the reporters is crucial to obtain more information about the adverse effect and to follow the development of the event and to clarify some misunderstandings. Another activity performed with collaboration of a colleague was the processing of adverse reactions and transform it in a line listing. I performed a weekly bibliographic revision in Portuguese journals. The objective of this revision is to find some adverse reaction related to Pfizer products in the literature that was not reported to the pharmacovigilance. I attended a presentation about periodic safety update report and discussion about its composition, and also a presentation about pharmacovigilance in clinical trials, since I had showed interest in continue my internship in the conduction of clinical trials. The report of all events is fundamental to continuously acquire more safety information about the drug, and basing on that do a benefit-risk evaluation. All the procedures to follow when an adverse event, a serious adverse event or a suspected unexpected serious adverse reaction occurs during the conduction of a clinical trial and all timelines that need to be followed were discussed.

2.4. Quality of Products unit

This unit is responsible for (2):

- Ensuring the quality, safety and efficacy of drugs and products that Pfizer provides;
- Ensuring its quickly availability for distribution to the market;
- Ensuring monitoring throughout the period of life, while in the supply chain.

The mission of this unit is to ensure the quality of drugs and products provided by Pfizer, whether for human or animal health, developing all necessary actions, strictly complying with all regulatory and internal requirements, while ensuring rapid access to people who need them.

Like in the other units I attended a presentation about the unit and its responsibilities. Releasing of batches of drugs, after the previous verification of the sample and analysis certificate, is one of the tasks performed. It was essential to be aware of the quantities in warehouse in order to have drugs available to enter in the

market. If something is not available in the market and in warehouse, as soon as it turns available its release to the market is crucial. A very good management is needed to maintain available all drugs.

Another activity developed in this unit is the management of quality complaints, its follow up and its registration in a specific system. Be aware of changes in drugs and have a broad knowledge in each drug is fundamental to promptly answer to all questions.

The revision of artworks in this unit concerned information about the price, bar code and the Braille information were another activity performed. The tool used was the same that in regulatory affairs unit. To do this, I had one document with all information needed to be in carton. Organizing the drug library was another task performed. The drug library has one sample of each batch of all drugs that are commercialized. I did the registry of new entries at the drug library.

2.5. Medical Information unit

The medical information unit's mission is to provide excellent medical information about Pfizer's products or on diseases related to them, through planning, development and implementation of programs and tools directed both for external customers or for internal order to ensure the safe and effective use of Pfizer products and support the therapeutic decision (2).

Tasks performed:

- Overview of the structure and functioning of the European model of medical information;
- Presentation of the medical information centre and its responsibilities;
- Presentation of the system used to do the management of scientific questions;
- Reading of applicable legislation applicable to medical information (e.g. copyright) (26);
- Sources of information and research methods of scientific information;
- How to prepare an answer to external customers – the structure to be followed and the information that can be given;
- Prepare an answer after research applying the techniques learned; and review the answers prepared.

2.6. Market Access

This unit is responsible for planning and implementing strategies, programs and partnerships with government entities and key customers in the area of healthcare, including scientific and professional associations, pharmacies and media, as well as the planning and implementation of financing and reimbursement (2).

Tasks performed:

- Overview of the structure and functioning of Market Access unit;
- Overview of programs and partnerships with different stakeholders;
- Reading of the applicable legislation (30, 31) for establishment of prices and reimbursement:
    - Decree Law no 106-A/2010, 1 October;
    - Ordinance no 1041-A/2010.
- Reimbursement policy – discussion about the establishing of the drug price and its reimbursement, how the procedure is carried out to obtain a price and reimbursement, what is the applicable legislation, and the importance of reimbursement in our days, since the drugs are more innovative and consequently more expensive;
- Preparing a request for a generic reimbursement, taking into account that the economic advantage for each generic drug for reimbursement purposes, after (and including) the 5th generic marketed, is established towards a retail price fixed at least 5% below the maximum retail price of the last generic whose reimbursement request was approved;
- Overview and discussion of pharmacoeconomic studies: cost-benefit, cost-utility, cost-effectiveness and minimization of costs. Reading some articles and exploration the pharmacoeconomic study for Inspra®.

2.7. Medical Affairs – Primary Care business unit

The mission of medical affairs of each business unit is to provide expertise and scientific knowledge to the cross functional teams, and other key partners, in support of strategies (2).

Tasks performed:

- Overview of the structure and functioning of Primary Care business unit;
- Presentation and definition of the positioning of medical scientific liaison and major responsibilities with regard to other areas / positions of the company. This role has several activities transversal to the whole company that starts prior to the obtaining of marketing authorization, prepare the medical community for the new drug, continue with its introduction in the market and finalize with its withdrawal. The medical science liaison is a professional with a bit of clinician (scientific knowledge) and salesperson (marketing knowledge) mixed in;
- Search about some drugs of other companies – study the market – and explore the possibility of co-licensing;
- Attendance of a cross functional team meeting (Inspra®) with the objective to verify the interaction of different elements from different units that work with the same purpose. In these meetings, the knowledge of each one is shared with the rest of the team, creating a good and creative work environment;

- Training in Lyrica® – this is one of Pfizer drugs. The training was given with the objective of having more information about this product and follow its development in different therapeutic areas;
- Attendance of the "XVIII Jornadas Internacionais do Instituto Português de Reumatologia" with the goal to contact with key opinion leaders.

3. Monodisciplinary internship

In this chapter I describe the CCO mission, gave some information to contextualize the activities performed and describe activities executed.

Monodisciplinary internship occurred in CCO, a Supporting Function unit, the unit responsible for carried out clinical trials in Portugal, since 2003. The main goal of this unit is:

"To undertake high quality clinical trials, contributing to the launch of effective and safe drugs and giving to our researchers' experience with these products prior to its launch in the market."

Rebelo, 2010 *(26)*

CCO has a team responsible for conducting clinical trials in Portugal and has an active voice contributing on evolution of legislation on clinical trials in Portugal. CCO is responsible for several activities, such as execution of feasibilities, conducting and monitoring of clinical trials.

In the framework of this unit I carried out conduction and monitoring activities from the perspective of a clinical trials monitor.

At the starting point of my internship, I needed to acknowledge the basic procedures of the company as well the procedures related to the monitor's role, before enrolling in any project related activity. The training process of monitor at Pfizer consists of 4 phases:

- Reading of Portuguese SOP and Guidelines described in CCO training curriculum;
- Performing trainings in an interactive web based platform called Power2Learn;
- Attendance in monitor workshop;
- Performing co-monitoring visits.

The training at CCO starts with the reading of company's SOPs which have the objective to promote guidance to the new members and collaborators of Pfizer. All collaborators need to be trained about rules, procedures and codes that rule their job. These SOPs are frequently updated. This way, during the internship some SOPs were read more than once, when they were updated. Apart from these SOPs, I was assigned to do a set of trainings in an interactive web-based platform called Power2Learn. The trainings in this platform were diversified; there were trainings of international SOPs and programs such ELARA, electronic case report form (CRF) and Rightrack II, useful tools in monitoring, etc. The trainings allowed me to contact for the first time with a variety of documents and tools necessary to perform my future tasks.

Training in GCP was approached in the set of web-based trainings. It was to crucial receiving training in GCP since these practices are fundamental for the execution of all monitoring tasks.

A monitor workshop was done in Paris and approached all relevant issues to conduct clinical trial monitoring. In addition to the theoretical component, the workshop had a strong practical component,

allowing the exchange of views with senior professionals, presentation of solutions for common findings and how to avoid them, and networking establishment, since there were professionals across Europe present in this event. The content of workshop covered all crucial topics to monitoring.

Monitor Workshop Content:

- Research and development foundations;
- Informed consent foundations;
- Investigational product foundations;
- Safety foundations;
- Selecting investigators and sites work process;
- Investigator meetings work process;
- Performing a site initiation visit work process;
- Clinical monitoring work process;
- Site closure work process;
- Audit and inspection work process.

In CCO I was allocated to different projects with the objective of cooperating in various stages of development of a clinical trial, since its submission and initiation, to monitoring and completion. The co-monitoring visits were done with a senior monitor. The different tasks performed are organized in the following phases:

- Planning and initiation;
- Monitoring;
- Closeout visit;
- Quality;
- Others.

3.1. Planning and Initiating

Planning and initiating a clinical trial consists in many activities, the majority of which involve completing the proper documentation and obtaining the necessary approvals to conduct the clinical trial. This phase involves communicating and working with the authorities and investigators. Documentation is critical to the clinical research process and all parts involved need to be aware of its responsibilities in order to open the site. The initiation process should be conducted efficiently and responsibly for the trial to start as scheduled since the subject enrolment cannot begin until all the initiation activities have been accomplished and documented (27).

Before discussing the activities in which I was involved in the initiation of a trial, it is important to have an understanding of four documents that are used in the planning and initiation of a clinical trial. They are:

- Investigator brochure;
- Protocol;
- Informed consent;
- CRF.

The information in the protocol specifies how the study is to be conducted and together with the investigator brochure and informed consent document it provides the monitor and investigator with the information necessary to conduct the trial. The CRF provides the investigator with a structured place to document the data gathered for the individual subject during the trial. It is important that the monitor understands each of these documents to be comfortable to discuss them with the principal investigator.

The activities performed at this level were regarding pre-trial visit, communication with authorities, site documentation requirements, investigator meeting, trial initiation visit and revision of essential document file.

3.1.1. Pre-trial visit

This visit is a key part of the investigator recruitment and selection process. However this does not indicate that the decision has been made by the sponsor to place a study at the investigational site.

As a monitor, I performed one pre-trial assessment (PTA), which has the purpose of ensuring that potential investigators meet the appropriate scientific and ethical standards and have the ability to carry out the proposed study according to the protocol, including the protocol-specific site requirements and ICH GCP standards. The PTA process is performed to evaluate, verify and document that the investigator is qualified, trained and suitably experienced to conduct the study, and that the site has adequate physical resources and staff to conduct the study. If some resources are not available, the monitor has the responsibility to find a solution if the site is a potential selected site to perform the trial. One common resource is the fridge or locked cabinets. It is important to be careful in the site selection process since we can compromise the protocol compliance and recruitment if the human resources are not qualified.

In collaboration with the investigator, I prepared the recruitment plan for the study taking in to account all specified protocol requirements, the hospital past history, and concurrent clinical trials, in order to obtain a number of possible patients eligible to enter into the study. It is essential to be realistic in this number because recruited patients are one of the metrics implemented in the CCO and it is preferable to appoint a lower number and recruit more than the opposite. It is not possible to guarantee numbers, but there are many ways to calculate a realistic number. Discussion with the investigator and the proof of past history are the essential tools to obtain it.

3.1.2. Authorities (regulatory authorities and ethics committee) review and approval / favorable opinion

The submission of the key documents to the authorities is very important to obtain an approval from them. There are some trial documents such as protocol/amendments, informed consent, safety information, and others that should be reviewed by the authorities. These documents are present in the initial submission to authorities done through a CTA format.

To carry out clinical trials in Portugal, the authorization of the INFARMED, CEIC and CNPD is necessary as well as the authorization of hospital administration boards. I carried out submissions to these authorities and institutions as explained in the following sections.

3.1.2.1. Submission to regulatory authorities and ethics committee

Submission process of a clinical trial to INFARMED and CEIC is done in parallel and through a package that contains:

- Presentation letter;
- Proof of tax payment to INFARMED;
- CD-ROM with the CTA with all required documents organized in folders and list J;
- Annex I filled (paper and electronic way).

To obtain the validation of request for authorization to run a clinical trial by the authorities, the request should be in accordance with the law. The sponsor should also ensure that the request has all elements required by law.

For the submission of CTA, the sponsor or the legal representative should present a requirement (presentation letter) to authorities with all required information, such EudraCT number, protocol number and title, and other relevant aspects, for example, if the trial is conducted in pediatric populations. All information sent to authorities should be listed in this requirement, for example, the proof of payment, the CTA, and other relevant documents.

Sponsor should also send a form which identifies the clinical trial and the entity and people responsible for the conduction of the study. This form, called Annex I is used in first submissions and contains all data set required for the submission. The Annex I describes all parameters of the study, since protocol and investigational product to legal representatives of the clinical trial in each country. The Annex I is obtained through the EudraCT web page, which is a database of all clinical trials commencing in the European Community. It has been established in accordance with Directive 2001/20/EC, and it is in this database that the sponsor can modify, validate, compare and save xml/pdf files of CTA to prepare a package for

submission to authorities. This file is sent in two formats to authorities, electronically in a CD-ROM with the CTA, and one copy dated and signed in paper with the request.

Since the submission is done electronically, the structure for the electronic submission is available in the web pages of authorities. This CTA presents several folders organized in different subjects in which the sponsor must put the applicable documents. These folders are recorded in a CD-ROM and sent with the request to authorities. The List J also must be sent with the request; this is a document checklist that helps to verify if all required documents for authorities are presented in the request.

The following two paragraphs do not belong in this section (Planning and initiating); however, I preferred to mention this subject in this section, with the first communication to authorities, because the procedure is similar.

The procedure to notify authorities of amendments to protocol is similar to the initial submission, however there are less documents involved. The notification of substantial amendments to authorities is done through a document entitled "Annex II", that can be found in the web pages of authorities. It is a detailed guidance on the request to the competent authorities for authorization of a clinical trial amendment. Annex II highlights the changes in the clinical trial since the last submission, and must be signed and dated. When an amendment is submitted to authorities, it is also necessary a presentation letter with relevant information, pay a tax, send all CTA folders only with the updated documents in CD-ROM, and the updated Annex I.

At the end of the trial, the Annex III must be sent to authorities. This document is a detailed guidance to the declaration of the end of the trial, describing the reason for the termination of the study. This Annex III is sent with one letter to authorities who introduce the notification of the end of the clinical trial.

Using all updated forms and folders that are available in the web sites of the authorities is considered a best practice; this way, there is no risk of submitting an obsolete annex, form or folder.

3.1.2.2. Submission to CNPD (National Data Protection Committee)

This committee evaluates if the data collected during the clinical trial compromises the integrity and privacy of the participants. The submission is done in a form available electronically in the web page of CNPD, which requests information about the purpose of data collection, what data are collected, if data is transferred for other countries and how the data protection is done. Some documents are sent to CNPD, such as CRF, in order to help with the judgment. This committee always put questions regarding the collection of data about the ethnicity of the subjects, so it is important to pro-actively justify why this data is important in the clinical trial in order to avoid questions and save time.

3.1.2.3. Submission to Hospital Administration Board

After we receive approval from all of the aforementioned authorities, it is necessary to obtain approval from the administration board of the hospitals. A folder with the following documents is submitted to the administration board for their evaluation: identification of the sponsor and investigator identification; regulatory authority, ethics committee and data protection national committee approvals; protocol; synopsis; informed consent; assurance certificate; principal investigator *Curriculum Vitae*; clinical agreement and financial agreement.

3.1.3. Site documentation requirements

During the site initiation, there are a number of documents that the sponsor must send to the investigator and that the investigator must send to the sponsor. Until the proper documentation has been completed and received by both parties, the investigational product cannot be shipped and subjects cannot be enrolled. I was actively involved in the process to get all documents from the site as well as prepare and send documents required.

The following documents were sent to the investigator:

- Sponsor-approved final version of the protocol;
- Prototype consent form document and/or consent form guidelines;
- Required regulatory documents (e.g. form FDA 1572);
- Approved investigator brochure;
- Financial disclosure information and/or forms;
- Signed agreements (e.g. confidential and financial agreement) between appropriate involved parties;
- Documents submitted to the ethics committee and regulatory authorities for consideration;
- Approval from ethics committee and any other documents given approval/favorable opinion, such as regulatory authority;
- Composition of ethics committee.

The following documents were received from the investigator:

- All required contractual agreements;
- Sponsor-approved version of the protocol, signed and dated by the investigator;
- Any written information to be provided to study subjects;
- Up to date *curriculum vitae* for the principal investigator and any sub investigator(s);
- Copies of applicable laboratory reference ranges;
- Appropriate financial disclosure information.

Most documents are forms that were personalized according to sites' information. However other documents needed to be created or translated to Portuguese. Regarding this last point, I performed the following activates:

- Translation and revision of translation of informed consent and informed consent for phamacogenetics, and exposure *in utero* document;
- Translation and revision of translation of synopsis;
- Preparation of documents to confirm the authorization of head of unit of hospitals where the clinical trial will occur, in this document the head of unit ensures that its unit has qualified human resources and facilities to run the clinical trial;
- Preparation of documents related with the infrastructure, research teams and equipment necessary for the processes of submission to the ethics committee;
- Development of the budget of one clinical trial for Portugal:
    - It was necessary to take into account all procedures present in the protocol, how many times they are performed, if are locally or centrally performed, and according to Ordinance no.839-A/2009, 31 July and Ordinance no.1320/2010, 28 December that establishes the price and tax to each procedure. It is also important to take into account other possible costs such as initial submission, amendments, materials, and others. The objective is to assign a cost for each patient per clinical trial, and according to the number of patients to be recruited, the total cost of the trial in Portugal.
- Preparation of clinical agreements:
    - This document states the obligations and responsibilities of the principal investigator and sponsor during the conduct of the trial;
- Preparation of financial agreements with the hospitals:
    - There are two options: the hospital has a template for financial agreements and we need to follow this template, or they do not have one and we use a Pfizer template. In both cases, we need to define the cost of each patient in the clinical trial in accordance to the current prices described in the law (Ordinance no. 839-A/2009, 31 July and Ordinance no1320/2010, 28 December). Before obtain the needed signatures in the financial agreement a good practice is the revision of the parts involved, in order to avoid issues and save time.
- Blinding plan:
    - Due to the specifications of investigational product and the protocol design, the development of a blinding plan is essential in order to ensure that all blind parts are really blind during the conduction of the study. The document provides both a generic and site-specific overview of the procedures and documentation necessary to maintain a regulatory acceptable level of blinding at the institution.

3.1.4. Investigator meeting

The investigator meeting is valuable opportunity to further enhance communication between sponsor and investigators. The meeting is organized by the sponsor and typically held at a central location. The meeting is a working session to promote consistency of practice among sites in a multi-center trial. The meeting serves as an opportunity to review the protocol, with emphasis on the inclusion and exclusion criteria, and the means used to capture trial data; identify and clarify responsibilities; review plans for recruitment of subjects and the difficulties to recruit; clarify all protocol procedures; review safety information regarding report of serious adverse event and adverse event. Provide information about the audit process is also discussed as well the publication issues. This is the opportunity to have the whole team involved in the clinical trial together, it is an occasion to establish professional relationships and supportive peer networks and reach a common understanding about all aspects of the study. The investigator's meeting is an opportunity for investigators to suggest some amendments if the protocol does not fit the usual care of the hospital or the guidelines and procedures of a particular country or unit.

I attended one investigator meeting. The goal of this meeting was to remember the investigators of them commitment regarding the number of subjects needed to recruit, since the recruitment rate was very low. All topics above mentioned were discussed, however it was very important to clarify some questions regarding the conduct of the study and the eligibility of subjects, share difficulties, issues, and challenges that other countries had and discuss and find possible solutions. It was very important because we meet all people with whom we usually "talk virtually" and I felt that we all share the same team spirit - working for the same purpose.

3.1.5. Trial Initiation Visit

The purpose of this visit, that I also performed, was to finalize the preparation of the trial in the form of a meeting. This meeting took place after receiving the regulatory authority approval. It was conducted by the monitor and attended by the site staff involved (27).

During this visit the following aspects were discussed: protocol (all protocol aspects must be discussed and clarified), informed consent, documents like: the investigator brochure, drug and laboratory supplies, signature sheet, CRF, adverse events, GCP, monitoring, procedures concerning audits and inspections and equipment.

Since the reporting of adverse events is a critical investigator responsibility, it was important to perform a more detailed discussion on important safety definitions, criteria and classifications.

This visit is for some trial staff the first contact with the protocol, so it is very important that all procedures are understood, questions are clearly answered and that after this visit the staff is able and ready to start patient's recruitment.

This visit is usually very tiring for the monitor as well as for the study team, so it is important that the monitor uses the best ways to capture the attention of the team. Henceforth, power point presentations and practical examples, such as the filling of CRF's, should be used by the monitor. After the visit, it is essential to carry out the elaboration of site initiation report, where we can describe what was discussed during the visit.

3.1.6. Essential Document File

Regulatory guidelines specify that the trial must be documented. This is achieved through the archiving of essential documents in site master file at site and trial master file at sponsor office. The documentation requirements allow the trial events to be recreated and also serve as an audit trail to verify the conduct and results of the trial. Site master file was sent to the site prior to the beginning of the trial, and can also be called investigator file. It is organized by tabs and contains copies of the documents that the site had sent to the sponsor and the sponsor to the site. The site then maintains the file, adding documents as appropriate. All required essential documents required must be filed in the investigator file before trial initiation. Any missing documents must be obtained and filed before enrolling the subjects. The list of essential documents needed before the clinical phase of trial starts is specified in ICH E6 (5).

During my internship I had the opportunity to organize these files, which gave me a continuous learning and training in one of the essential activities that a monitor has to perform in his day-to-day work in order to perform a good monitoring. A study generates a huge amount of documentation. I needed to make sure that they are all are correctly archived. Archiving a document on a wrong file can have unintended consequences. The monitor should have a good working method for the preparation, organization and updating of these files.

It is very important during the conduct of the trial to verify if all forms/logs implemented are the updated version, and when new versions are implemented, it is essential to document the transition from the old forms/logs to the new ones. When something is not in the file, it is good practice to write a note to file explaining why this happens (note to file).

3.2. Monitoring

Monitoring by the sponsor is a requirement of ICH GCP. Monitors are extremely helpful to the investigator and the site staff since monitors can provide valuable insight on the site's performance in conducting the trial and they are also an excellent resource that can share their knowledge and expertise with the site staff.

On-site monitoring visits are conducted at regular intervals after the study is initiated. Frequency of visits is determined by a number of factors, such as study design, length of study, complexity of study, recruitment/enrolment rate, sites compliance with the protocol and, the experience with clinical research. The monitor oversees the progress of a clinical trial and ensures that it is conducted, recorded and reported in accordance with the protocol, sponsor SOP, ICH GCP guidelines and applicable legislation.

3.2.1. Site-monitor communication

Site visits provide opportunities for the investigators to discuss trial issues with monitors. It is important to maintain regular contact with the site via telephone, letters, mails and/or faxes. These communications confirm the study progression at the site, address problems (if any), and inform the site of upcoming on-site monitoring visits. All essential communications must be recorded and all pertinent issues must be discussed face-to-face with the clinical trial staff.

3.2.2. Protocol adherence:

Protocol has all procedures to produce data that is needed to achieve the objectives. It is important verify if all procedures were done as well as verify the GCP compliance.

As monitor I:

- Verified if the investigator was following the approved protocol and any approved amendments through the completion of CRF and the verification of source documents. If the investigator was not compliant with them, it is important to report the deviation, escalate the issue, if serious, and implement corrective and preventive actions in the site, like re-train the site.
- Verified if the investigator and other staff members were performing their specified functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator, and that these functions were not delegated to unauthorized persons. The investigator needs to be aware that he can delegate tasks but only if the people have training and can prove it. Putting some questions to the team is an optimal strategy to know if they are doing something that is not delegated to them.
- Verified if all adverse events were appropriately reported within the established time periods, through a continuous monitoring (at site or remotely) of clinical trial data. To ensure that patient's

are properly taken care when they come the centre, a good organization is crucial. In this way, I knew when was needed verify the data collected.

- Ensured the blinding. Blinding is one method to avoid the bias in clinical trials. Maintaining the blind in a study with a third party unblinded is a challenge, because a bad blinding plan can compromise the integrity of collected data. Development of structured documents helps to avoid errors between blinding and unblinding parts and this way, maintaining the blind till end of the study.

3.2.3. Subject recruitment

Informed consent is a process by which a subject voluntarily confirms his/her willingness to participate in a particular trial. It is important that before signing the informed consent the patient has been informed of all aspects of the trial that are relevant to the subject's decision to participate, to have opportunity raise all kind of questions and these are clarified. Informed consent is documented by means of a written, signed and dated informed consent form.

In my monitoring activities I:

- Verified if written informed consent was obtained from all subjects prior to their participation in the trial and, when applicable, verified if all amendments were signed and dated; and if the information regarding the participation of the patient was recorded in the patient file. If a subject refused to sign an amendment or, decide to withdraw from the study, the investigator should accept the patient decision and record the reason of withdrawal in the patient file, only this way I could verify the reason for the patient withdrawal.
- Verified if the investigator enrolled only eligible subjects. A clear and complete history in the patient file is essential to check its eligibility, and avoid issues in audits. Therefore it is important that the investigator is aware of this fact and has all data needed to confirm the patient's inclusion.

3.2.4. Drug Accountability

All drugs should be recorded in specific forms according to the procedure done. "These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.(5)"

At this level I had opportunity to:

- Verify if the investigational product was stored in a secure place; ensure that the drug was stored at the recommended temperature, through the verification of temperature logs that register the

temperature and its deviations. Verify if the drug was administered only to eligible subjects and in the correct doses, according to the protocol requirements through the revision of accountability logs. This document gathers all the information (e.g. number of container, dosage) regarding the investigational drugs dispensed to the patient.

- Verify if the reception, use and return of investigational drugs was adequately documented through the verification of the forms and, cross-check with the information available for the monitor that states how much study drug was received, prescribed and returned. It is crucial the filling of these documents because, they allow me to know where the study drug is and, if the recorded data are in accordance with the data made available to the monitor; so that he/she can perform the drug reconciliation. This is an accountability process that takes into account the drug sent to site, given to patients and sent for destruction, with the objective to know if some container of investigational drug was lost.
- Destruction of investigational product: unused, used and expired. This process must be adequately documented. A detailed report of the study drugs that are sent for destruction helps the monitor in the drug reconciliation process.

3.2.5. Record keeping

All data generated during the trial must be kept as well as all correspondence between the centre and the sponsor. The monitor plays an important role in this task.

As a monitor I:

- Verified if source documents and other trial records were accurate, complete, legible, updated and adequately maintained, with the objective to compare with data entered in the CRF. If any data is missing the investigator should justify or complete the file.
- Performed source data verification between data entered in CRF and data in clinical registry. This verification had the objective to confirm if all required data were collected and recorded adequately in CRF.
- Collected CRF in paper and other documents for the evaluation of endpoints, in accordance with protocol requirements. The omission of the identity of patient always that medical registry is collected is very important. Only the patient identification number must identify the subject in study.
- Solved discrepancies of electronic CRF and paper CRFs and filling of transmittal form. This transmittal form is the way to track documents sent in paper to data managers.
- Verified if essential documents required by ICH GCP, SOP's, and applicable legislation were retained with an intensive revision of the site master file. I verified, for example, if the all versions of informed consent are present, and safety letters are completed and correctly archived. To execute this activity I created a check-list with all documents required and if applicable all versions of documents to help me to do this verification, in a practical way.

At the end of monitoring visit, I often reviewed the findings with the investigator and/or study coordinator. This discussion includes those areas in which the site is performing well, areas in which there may be a need for improvement, corrective actions that may need to be implemented by the site, and any follow up action items. To finalize, I documented the findings in a written report.

3.3. Site close out

Study site closeout consists of a series of activities that mark the end of the various aspects of study conduct.

Site close out activities must be performed on study sites when one of the following applies(27):

- When subjects at the study site have participated according to the protocol, no further subjects will be recruited and no further data will be collected.
- When the study site has been initiated and subsequently cancelled prior to any subjects being enrolled into the study.
- When recruitment of new subjects at the study site has been stopped prematurely, and there is no intention of restarting the study.
- When the study was no longer approved by the authorities.

When there is a decision to stop the study, authorities should be notified through the filling of Annex III as explained in section 3.1.2.1.Submission to regulatory authorities and ethics committee.

Study site closeout involves activities both at the site and at the sponsor's location. The tasks that I have performed had the purpose to ensure the following:

- All study data had been collected;
- No more data is required to be collected per protocol with the verification of CRF;
- Investigators records were complete, and the records management and retention processes had been discussed and implemented, as appropriate;
- The investigator file was complete and ready for archiving according to ICH GCP and applicable sponsor and local requirements, and for example, when required per protocol, archive some specific documents, such as imaging tests; to ensure this a depth revision of investigator file was carried out;
- All study drugs had been accounted for and all unused supplies had been returned, or arrangements for their return or destruction had been agreed upon;
- If drug was destroyed, certification of destruction is necessary. At this point, all drug reconciliation was performed, with all documents filed during the clinical trial;
- Supplies (e.g. paper CRF) and equipment had been collected, or arrangement for their location had been made.

At the end of close out visit, I discussed with the principal investigator the site's post-trial responsibilities regarding final accountability for study and drug supplies; record retention; and providing post-closeout information, like resolution of queries. This discussion was registered through a signed close out letter.

It is important that before the close out visit, one monitoring visit is carried out with the purpose of verifying if all documents are archived in the site master file. This visit is like a pre close out visit to prepare the closing of the site.

After the close out visit, it was important to document the close of the site through a close out report; and update all tools used to monitor the trial.

3.4. Quality

CCO has a quality plan implemented. Implementation guidelines are one of the tools that help all elements in the unit to perform their work in a standardized form. Audits are a tool of continuous improvement and metrics is another tool used and help the monitor to manage his/her work since they allow to assess the workload and performance of the team, the timings of local authorities and other entities approvals to start a clinical trial, the quality of data reported and collected, the compliance with ICH GCP and SOPs, and our competitiveness versus other countries (28).

3.4.1. Audit

An audit is defined in ICH GCP, as "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, SOPs, ICH GCP, and the applicable regulatory requirement(s)" (5).

In the scope of an audit, I performed the following activities:

- Implementation of corrective actions and preventive actions after the audit report with the objective to prevent the finding in the future;
- Development of plan of actions as an answer to the findings of audit after discussion with investigator. This plan includes also preventive and corrective actions.

3.4.2. Development of a guideline to elaborate informed consent and template of informed consent document

The guideline developed states the need to describe and document local procedures to ensure that informed consent documents are handled according to appropriate quality standards. This guideline has three templates associated. The objective of each template is to put standard information in one single document, in order to establish a standard model of informed consent that can be used regardless the therapeutic area of protocol. The following templates were created:

- Phase I
- Phase II/III/IV in adult population
- Phase II/III/IV in pediatric population

These templates were based on English templates and they were elaborated in an easy language to be comprehensible to all people. They have information regarding the Portuguese legislation and standard contacts (for example, the ethics committee contact) that can be used by the patient.
The template has a set of rules that helps the monitor when he/she is developing an informed consent, indicating what the required information is and where they can find it.

3.5. Other activities

In this section I describe other activities performed that were transversal to all clinical trial, tools used and conferences attended.

3.5.1. Prompt monitoring report expert

Prompt monitoring is the consistent and timely review of the electronic CRF in the clinical database during the conduction of a clinical trial. This review of data is performed remotely and has the same purposes as the monitoring. However, in this case the monitor needs to be critical and judge the information entered in CRF without source documents. This report needs to be performed in 15 calendar days since the data are entered in CRF; unless the monitor visits the study site, in 15 days.

The purpose of this report is to:

- Ensure timely review of subject data concerning subject safety, protocol and ICH GCP compliance;
- Check that the data required by the protocol are reported accurately on the CRFs;
- Check that the dose and/or therapy modifications are well documented for each of the trial subjects;
- Check that adverse events, concomitant medications and inter-current illnesses are reported in accordance with the protocol on CRFs;
- Determine whether all adverse events are appropriately reported within the time periods required by GCP, the protocol, the ethics committee, the sponsor, and the applicable regulatory requirements;
- Check that the visits the subjects fail to attend, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs;
- Check that all withdrawals and products of enrolled subjects from the trial are reported and explained on the CRFs;
- Inform the investigator of any CRF entry error and issues in a timely manner;
- Promptly address potential issues in the conduct of the clinical trials and escalate them appropriately;
- Proactively follow-up issues and, as needed, retrain the site staff on protocol-specific requirements or procedures.

There is a specific web-based tool that identifies all pages that were entered and completed in CRF by the study staff and need to be verified. I learned to work and manage this tool in order to obtain all pages in the CRF that need verification. Reading of guidelines and presentations were essential to understand how this tool works. This is a complex tool that has some requirements that need to be followed to obtain the right results. After understanding how this tool works, I shared the procedure with my colleagues, since this was a report that nobody understood how to obtain.

3.5.2. GCP training

I gave GCP training to the staff of a vendor. This training was given during the conducting of a clinical trial and the goal was to prevent future issues regarding the records retention. GCPs were explained, all responsibilities were discussed and especially, all applicable topics to this staff and all questions were clarified. To prepare this presentation I used the ICH GCP (5).

3.5.3. ELARA

ELARA is a global document repository designed to store ICH essential documents and Pfizer essential documents, thereby enabling staff to readily identify which documents are in the trial master file. These documents result from the correspondence between the sponsor and investigator. They are uploaded to the ELARA system, and it was my responsibility as monitor to perform a quality check (QC) to all documents introduced locally. Document QC is the process that determines whether the documents have been indexed correctly, are filed in ELARA correctly, that the upload was successful and have all required information.

3.5.4. RighTrack II

RighTrack II is the global web-based application used for entering, maintaining, viewing and reporting clinical trials registry data. This application has all Pfizer protocols and sites of each protocol and has also a list of all contacts of people involved in the protocol.

This tool helps to maintain the status of sites, the list of active investigators and not-available investigators, tracking the clinical trial application, tracking all data regarding informed consent and protocol deviations, and it is through this tool that all reports resulting from monitoring visits were performed.

3.5.5. Conferences

I attended the following conferences:

- Avaliação de Tecnologias de Saúde em Portugal: Perspectivas, Aibili, 21st January 2011
    - In this conference the need to evaluate health technologies and how it can be done; and the need to create an entity responsible for this evaluation or the delegation to a created entity was discussed.
- 6º Encontro Anual "Ensaios Clínicos" – 25th January 2011
    - In this conference, the state of the art of clinical trials were discussed and a variety of issues was approached, such as clinical trials with orphan drugs, the centralized submission of clinical trials in Europe, feasibility process, audits and others issues important to clinical trials.

4. Discussion

In this chapter I discuss the activities performed during my internship as well as the competences and skills acquired during these 9 months.

In the following paragraphs I present acquired competences that were transversal to all internship.

As a professional in a pharmaceutical company, it was essential to understand how the company is organized and how each unit adds value to the business. Keep abreast of market knowledge and analyze information concerning company products; competition (other companies), and customers is also useful to be aware of the difficulties, challenges and earnings. Only this way I could understand the impact of my work in the company.

As a Pfizer collaborator, the reading of SOPs and the trainings received were essential to know how to work according to standards of conduct and ethics of Pfizer. This way I can show my commitment with Pfizer's mission and values.

During the internship, it became a fact that every time an idea is presented, it must be supported with facts and arguments (do not identify a problem if you do not have a solution). An idea well-structured is half step to obtain an approval. This assumption also applies in making decisions. It is easier if they are based on logical assumptions that reflect factual information.

Performing presentations allowed me to develop my verbal and non-verbal communication skills including, where appropriate, the use of software tools. Being a good listener and using well thought arguments and the power of persuasion to influence, and present ideas were essential in the interaction with other units and investigators.

One important achievement was to understand that working in cross functional teams facilitates access to expertise and best practice of each element. This way the objectives are achieved more quickly.

In the following sections 4.1. and 4.2. I discuss in detail the multidisciplinary internship and the monodisciplinary internship, respectively.

4.1. Multidisciplinary internship

Once my internship was "personalized" due to this multidisciplinary phase, the structure presented and the coordination with the managers of each unit, allowed us to adjust the activities to the time that I spent in each unit. Whenever needed, and if I was interested, it was possible to spend more time in one unit.

It is important to recognize that in each unit I had the support of all team members. All managers and officers were available to teach me with the best of their knowledge in spite of all work that they had to do. I experienced good environmental and team spirit in each unit, and between them, conveying that everyone is working towards the same goal.

Pharmaceutical industry is much regulated, and it was possible to observe it when I was in the Regulatory Affairs unit. The activities carried out in Regulatory Affairs and described in section 2.2.Regulatory Affairs unit, showed me what legislation rules the pharmaceutical industries, and showed me one side that I did not know – the strategic side – and how we can take benefits from the legislation. Another interesting activity was to verify if there are patent infringements to Pfizer patent protected drugs. The constant contact with regulatory authorities was another point that I observed and the good environmental between these two entities brings benefits to both parts.

Clinical trials are not enough to collect all safety information regarding the experimental drug, so the pharmacovigilance is responsible for the management of safety information after the marketing authorization. The activities performed and described in section 2.3.Drug Safety unit, showed me why it is important to report an adverse event and how useful the information collected to evaluate the risk-benefit of drugs can be. Due to the specific trainings needed to perform tasks in this unit, I did not develop practical exercises there. However, a strong theoretical component was given to understand the purpose and activities of pharmacovigilance.

The Quality of Products unit was totally new for me, and showed me, as stated in section 2.4.Quality of Products unit, all activities needed for drugs to arrive to the pharmacies, as well the management of quality claims. In this unit, I experienced the impact of legislation (withdrawal of drugs' prices from the carton) in the "usual" work and what was done to solve the issue. It is a very active unit since it is correlated with the stock management, where each day has different things to do.

The activities performed in the Medical Information unit, section 2.5.Medical Information unit, showed me that the drugs have more potential and uses that we think they are. There is a variety of scientific questions with purpose that need to be explored. The questions of off-label prescriptions are huge and require a detailed research and this information can only be given to healthcare professionals. This unit is an important tool available to healthcare professionals and the general population and can improve the correct and safety use of drugs.

In the Market Access unit, the activities that I carried out, described in 2.6.Market Access, showed me that for drugs to be recognized as different from their competitors, it is essential to show therapeutic value and economic advantage in our days, turning them into successful drugs. The tasks I performed allowed me to contact with all legislation that regulates this area as well as some publications showing the need of economic advantage of drugs. Another important issue approached in this unit was the social responsibility that Pfizer has. They have concerns with the public health that they try to solve with social programs and others initiatives.

Medical Affairs has grown into an increasingly critical function. A well-structured medical affairs launch strategy can help informing important stakeholders regarding the promise of an upcoming drug. The activities performed, trainings received and the conferences attended in the Primary Care business unit described in 2.7.Medical Affairs – Primary Care business unit, allowed me to understand the strategic function of a medical affairs team. The short time spent in this unit allowed me to have a picture of the role of a medical scientific liaison. This role is interesting because it combines the scientific knowledge with strategy to obtain good results. This is one area of interest for me that I intend to explore in the future.

Planned calendar had suffered some alterations in order to start as soon as I could in CCO, so I did not have the opportunity to spend some time the Quality of Procedures unit. This is an area of my interest since it is transversal to the entire company and carries out tasks where I would like to have/acquire some knowledge.

4.2. Monodisciplinary internship

Monodisciplinary activities described in chapter 3.Monodisciplinary internship, allowed me to develop my knowledge in the conduction of clinical trials and acquire competences.

All activities performed in the CCO unit allowed me to improve my knowledge about all stages of development of a clinical trial and also allowed me to understand the impact of clinical trials in the development programs and why their execution and monitoring are so important.

All tasks performed in the conduction of clinical trials need in accordance to local SOPs, ICH GCP and applicable legislation. So, the complete understanding of the trainings was essential to perform a structured work. For example, a misunderstood training can lead the monitor to carry out a procedure incorrectly, or even not doing it at all. All activities that I performed during the monitoring visits and even the activities developed in the office showed me how important it is that everything is recorded. Only this way we can prove that it exists, and it is crucial to ensure the tracking of everything done during a clinical trial.

Being a monitor is to ensure that the safety and rights of the patients are protected and that the study is carried out in accordance with the protocol and with all applicable regulatory and/or ethical requirements. To ensure this, a lot of documents and forms are involved, that need to be organized and archived in accordance with sponsor's specifications as described in section 3.1.6.Essential Document File. In order to ensure that

everything can be re-constructed, all of these documents must contain all of the required information. It is my function to verify if the all the information was collected. During monitoring visits, organizing these documents was a hard activity since there are several documents and they have a specific place to be archived. However, this activity was also challenging, since my purpose was to maintain the files updated without missing information. In the close out visit, all required documents must be archived in the investigator file. I implemented, as a good practice, the performance of one visit prior to the close out with the objective to carefully review all files and record the missing documents. At the close out visit I had the opportunity to archive missing documents.

The monitoring visits to sites allowed me to put in practice everything that I had learned during the trainings and co-monitoring visits. I verified how difficult the compliance of sites can be if they do not have a good organization, and here, the monitor assumes an important role to ensure the safety and rights of patients and the quality of the collected data.

I had the opportunity to work with sites with a strong organization (infra-structures and human resources) and the opposite. I can conclude that a structured, experienced, trained and motivated team is able to conduct the clinical trial more easily according to all requirements and achieve the objectives earlier. Differences are visible between these sites, and the work is easier in sites where a “clinical research culture” is implemented and more challenging in the other sites. In spite of these differences, my work was performed with same depth in both kinds of sites.

The development of reports after each monitoring visit was a useful tool to register what I had done in the site and what were the pending issues that needed to be solved in the next visit. I also developed monthly reports during my internship. With this activity, I detailed what I had done in the month and which activities I would perform in the next month, planning it ahead.

Due to the different activities in different protocols, the establishment of deadlines, timetables, metrics and specific actions are precious tools that help me to achieve the desired results. Another skill that I acquired was to proactively identify problems and always seek for additional resources to get things done - never give up. Planning all activities to be done is a good exercise to act quickly as well as clarifying the difference between what is important and what is an immediate priority, I.e. not treating everything urgent as equally important and understand the need for a balance between 'the need to get it done now' and “the need to get it right”. Set priorities straight through effective planning and time / resources management, but do not forget to be flexible in the approach to work, and readily adapt to change.

“Thinking out of the box” was essential to contribute with creative ideas and new ways of doing things in times of change and when we found difficulties that needed to be overcome.

At the beginning, I had the opportunity to work with senior monitors. With time, I became independent, demonstrated an "I am accountable for" attitude and committed to the successful delivery of the project/task with minimal supervision. However, every time I performed a new activity, I sought help or feedback from

senior monitors. Being aware of my competences was essential to continue developing good work, so I proactively sought to address gaps in my competence requirements and actual performance. During the internship, I verified that I am a curious person and motivated enough to take initiative to learn more and acquire new skills and transmit this information to my colleagues and maintain a good environment, as happened with the prompt monitoring report.

Starting to work in a clinical trial which had already been monitored by another monitor is a task with some challenges, because I did not know what is the actual status of the sites, what could be found there and what was missing. For me, it was very important to carry out handover visits. However, in my opinion, one single visit was not enough to have an idea of the real status of the sites. So, my suggestion is that there should be at least 2 handovers visits, with different purposes, one to give an overview of the protocol procedures and other to verify the organization of all documents, in order to file all missing documents and solve all pending issues before the clinical trial was picked up by the new monitor.

Interaction with other units, mainly the Regulatory Affairs and Drug Safety unit and investigators (site staff) helped me to understand the multidisciplinary network that needs to be arranged in order to successfully conduct a clinical trial. Although not physically present, all study team behind a clinical trial is essential to achieve the objectives and to conduct it successfully. So, an effective communication is important to assure that everything is understood. Another important interaction is the interaction with the CCO team, I developed tasks not usually performed by the monitor with the objective of being independent enough and, when needed, to help the unit to carry out these activities. Here, the experience of my colleagues was essential to avoid some mistakes and being prepared for possible issues and, in advance, presenting possible solutions.

The contact with investigators during the internship was a network that was progressively built. Since the clinical research is carried out during the clinical practice, the majority of investigators do no dispend much time with clinical research, so the permanent contact with them through different ways was essential to discuss any problem. In-person meetings are preferable whenever possible.

The submissions performed to authorities in the planning and initiating phase of a clinical trial, described in 3.1.2.1.Submission to regulatory authorities and ethics committee, showed me how bureaucratic the process can be and that it takes much time to obtain approval when comparing with other countries. A deep review of all documents submitted to judgment is essential to obtain a valid process. So it is very important be aware of all requirements of the authorities to do a good work. The submissions performed to hospital administration boards allowed me to conclude that a standard between hospitals does not exist, and the approval time is an example of that, since the hospitals have different approval times, ones are quick while with others it is necessary to remind them about the process.

During my internship, what I enjoyed the most was the contact with different people and the establishment of networking and friendships, with which I know that I could count in the future. The good environment at

work and in activities, like teambuilding, was also essential to develop a good work. Seeing our work recognized is fundamental to continue to develop a good work and it motivated me to improve what I had been doing.

What I enjoyed less was the lack of time that the investigators assign to clinical research, since the whole team (sponsor and investigators) is working for the same purpose. It is frustrating to be dependent of people who always say that do not have time, when they had accepted to carry out and have clear responsibilities in the clinical trials. However, I cannot generalize, because there are good investigators who care with clinical research. It is, for me, a challenge to attract the investigators to the clinical research, showing them the advantages of carrying out clinical trials.

According to the information described in the section 1.4.Clinical Trials in Portugal and my experience in clinical trials, I identified some gaps and challenges in clinical research in Portugal. Early clinical trials phases were not performed and there is a poor academic initiative in clinical research. There is lack of organized structures with a clinical research culture implemented to carry out clinical trials; this way is hard to conduct clinical trials. On the other way, the hospitals do not show motivation or interest in carry out clinical trials, and have a complex and bureaucratic process of approval as I verified in the submission process to administration boards and it is not harmonized between hospitals.

Carrying out clinical trials has advantages for the country, since the drugs and diagnostic exams are paid by the sponsors. The patients had opportunity to have access to innovative drugs before their marketing authorization, and the investigators have opportunity to improve their knowledge and experience in clinical trials. Other advantage is the benefits of clinical trials in the host economy, since they are a number of stakeholders in which clinical trials have impact. They also allow the education & professional development of researchers, offer employment opportunities and transfer new technologies and know-how to institutions. Portugal needs to become a country eligible to conduct clinical trials again since they have huge advantages that we cannot lose.

I present the following ideas to help Portugal overcoming this situation. Give training and clarification sessions to hospital administration boards in order to incentive the clinical research in Portuguese hospitals as well as incentive clinical research across the entire health system. Sponsors should promote events and training sessions to hospitals less able to carry out clinical trials. Create an entity (research groups) in the hospitals responsible for the evaluation of clinical trials in order to facilitate the approval process. Development of specialized centers to conduct clinical trials with a specialized and trained infrastructure and invest in centers for phase I is other suggestion where Portugal can make the difference. Allow the publicity to clinical trials providing information to all population. Establishment of partnerships between pharmaceutical companies and academic institutions, the companies can share its experience to academies in order to increase the number of clinical trials carried out by academies. Give training in clinical research during the degree of future investigators.

5. Conclusion

In conclusion, after 9 months of experience and according to objectives presented in the introduction, I feel that they were achieved / accomplished.

The objective of the multidisciplinary internship was to acquire basic skills to work in each unit. After the experience in each unit, I realised that my degree have given me a multidisciplinary background and training making me able to perform the activities with some additional training. So, I concluded that the Master's in Pharmaceutical Biomedicine allowed me to work in any one of these areas depending upon my personal skill set and interests. In spite of I have not had the opportunity to spend some time in the Quality of Procedures unit; I feel that the objective was achieved through the experience gathered from the others units.

Regarding the monodisciplinary internship, all work performed at sites or in the office allowed me to understand how a clinical trial must be conducted and what are the skills that a monitor should have. I realised that the world of clinical trials without previous training is hard and challenging. Therefore, the complete understanding of the trainings was essential to perform a structured work.

The continuous contact with investigators, Pfizer units and institutions allowed develop a network of contacts that I can use as reference in the future.
All activities performed, problems solved and managed and experience helped me to develop my skills. The less positive experiences allowed me to acknowledge my weaknesses and work on them, in order to avoid the same issue in the future and to strengthen my skills.

During my internship, I gained very clear notions of what are the functions of a clinical trials monitor and its role in the development of a drug; how CCO contributes for the Pfizer development; all the efforts done by Pfizer to get safe and efficacious drugs available to the population and I understood that the pharmaceutical industries are much more than companies that sell drugs. They have concerns with the public health that they try to solve with social programs and others initiatives.

It was also important to verify the current state of clinical research in Portugal, and that clinical trials are a source of investment that Portugal has been losing to other countries for quite some time. This is also an opportunity that is lost for the Portuguese patients and investigators to gain earlier access to new drugs that can make a huge different in their lives.

After 9 months, I fell that I have evolved personally and that I obtained enough knowledge and experience to ingress in the working world. In the future, I would like to continue to work in this area, but in another position, something more challenging, like the study manager position. Areas like Clinical Development and Medical Affairs are other possibilities that I would like to experiment. in conclusion, my objectives for the future are the continuous improvement of my skills and acquiring knowledge to be able to carry out any work of my interest.

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