Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2011

FILIPA RAQUEL OLIVEIRA FIGUEIREDO

RELATÓRIO DE ESTÁGIO CURRICULAR NUMA CRO E INDÚSTRIA FARMACÊUTICA

CURRICULAR TRAINING REPORT IN A CRO AND PHARMACEUTICAL INDUSTRY

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Relatório de Estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Professora Doutora Susana do Carmo Salgueiro Bule, Professora Assistente Convidada da Universidade de Aveiro e Diretora Executiva da Eurotrials, e da Professora Doutora Maria Joana da Costa Gomes da Silva, Professora Adjunta da Universidade de Aveiro.

Dedico esta experiência à minha Família, em especial aos meus queridos pais, irmão e Tiago, tão especiais, tão presentes e sem os quais muito pouco faria sentido.

O JÚRI

presidente

Doutora Alexandra Isabel Cardador de Queirós
professora coordenadora da Escola Superior de Saúde da Universidade de Aveiro

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PALAVRAS-CHAVE Estágio, CRO, Indústria Farmacêutica, Ensaios Clínicos, Monitorização

RESUMO

O presente documento relata a minha experiência de 10 meses enquanto estagiária na Eurotrials, Consultores Científicos, uma *Clinical Research Organization* (CRO) portuguesa em expansão e, posteriormente, na Roche Farmacêutica Química, uma das indústrias farmacêuticas líder na área da saúde.

Esta experiência, que decorreu entre Setembro de 2010 e Julho 2011, teve uma vertente multidisciplinar e monodisciplinar, o que me permitiu colocar em prática uma grande porção de conteúdos apreendidos nas disciplinas que compõem o Mestrado de Biomedicina Farmacêutica da Universidade de Aveiro, possibilitando a aquisição de variadas competências tanto a nível pessoal como profissional.

Durante este período acompanhei inicialmente 9 ensaios clínicos como *Clinical Research Associate* (CRA) *trainee* e, progressivamente foi-me dada a oportunidade de realizar tarefas de forma mais autónoma e, consequentemente, de acompanhar 3 ensaios clínicos como CRA. Terminei o meu estágio curricular a desempenhar autonomamente todas as funções inerentes ao trabalho de um CRA.

A elaboração deste relatório pretende descrever as atividades desenvolvidas ao longo de todo o estágio, bem como, dificuldades sentidas e aprendizagem consolidada. Para além disto, pretende também dar a conhecer a minha visão pessoal sobre o papel do CRA na condução de ensaios clínicos e os possíveis desafios a superar tendo em vista a continuidade de Ensaios Clínicos em Portugal.

KEYWORDS Training, CRO, Pharmaceutical Industry, Clinical Trials, Monitoring

ABSTRACT

This document describes my 10-month experience as trainee at Eurotrials, Scientific Consultants, an expanded Portuguese Clinical Research Organization (CRO) and later at Roche Pharmaceuticals, a pharmaceutical industry leader in healthcare.

This experience, which took place between September 2010 and July 2011, had a cross-disciplinary and mono-disciplinary strand, which allowed me to put into practice a great deal of content learned in the disciplines that make up the Master of Pharmaceutical Biomedicine, University of Aveiro, enabling the acquisition of several skills, both personally and professionally.

During it was given me the opportunity to follow 9 clinical trials as Clinical Research Associate (CRA) trainee and gradually it was given me the opportunity to perform tasks more autonomously and hence to follow 3 clinical trials as CRA. I have finished my curricular training being able to perform autonomously all tasks of the CRA job.

The preparation of this report intends to describe the developed activities throughout the training, as well as encountered difficulties and consolidated knowledge. In addition, also intends to disclose my personal view on the role of CRA in the conduction of clinical trials and the possible challenges to overcome in order to continue clinical trials in Portugal.

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ABBREVIATIONS LIST

AE	Adverse Event
CEIC	*Comissão de Ética para a Investigação Clínica* - Ethics Committee for Clinical Research
CNPD	*Comissão Nacional de Protecção de Dados* - National Committee for Data Protection
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CT	Clinical Trial
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
CV	*Curriculum Vitae*
DM	Data Manager
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde I.P.* - National Authority of Medicines and Health Products
IRB	Institutional Review Board
ISF	Investigator Site File
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
PhF	Pharmacy File
PI	Principal Investigator
PRO	Patient Reported Outcomes
R&D	Research and Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedures
TMF	Trial Master File

1. INTRODUCTION

This document reports the curricular training is part of the educational program of Master's degree in Pharmaceutical Biomedicine and was passed in two institutions: Eurotrials, Consultores Científicos (Eurotrials), a Portuguese Contract Research Organization (CRO), and F. Hoffmann-La Roche Ltd. (Roche), a Swiss global health-care Company, on a pharmaceutical division. I initiated my curricular training on Eurotrials since September 6th 2010 to April 15th 2011. In February 2011 I accomplished Eurotrials requirements to be appointed as CRA. Since this promotion, I was able to work autonomously.

Then, an opportunity arose to go to Roche, under Eurotrials responsibility, where I stayed from April 18th 2011 to July 06th 2011.

In this report a characterization of the host institutions will initially be made. Then, the general training and specific activities, as well as the knowledge and experience acquired during my curricular training will be described. Furthermore, a discussion about my experience and encountered difficulties, as well as a brief comparative analysis, based on my ten-month experience, between working as CRA on a CRO (Eurotrials) and on a Pharmaceutical Industry (Roche) will be described. Finally, a conclusion about my whole experience will be presented.

1.1. VISION ABOUT THE INSTITUTIONS – EUROTRIALS & ROCHE

1.1.1. EUROTRIALS

Eurotrials, Consultores Científicos, is a privately owned company founded in Lisbon in 1995 whose activities are focused on scientific consulting in the health area and clinical research (1).

Eurotrials had a rapid and sustained growth and currently it operates in Europe, Latin America and Africa. This is, an office in Brazil was implemented since 2001 and it was started activities in some countries of Portuguese Speaking Africa in 2004 (1).Following this, in Figure 1 it is represented the overall structure of Eurotrials Portugal with ten main activities represented: Research & Development; Clinical Trials; Epidemiology & Late Phase Research; Data Management; Biostatistics; Regulatory Strategy & affairs; Pharmacovigilance; Quality and Teaching and Training (1).

Currently, in Portugal it has a team of over 80 employees and includes physicians, biologists, pharmacists, biostatisticians, sociologists, nutritionists, chemists, engineers, psychologists and mathematicians, among others. In my opinion this is very worthwhile especially since many times this interdisciplinary allowed interesting brainstorms and also useful trainings carried out by employees who dominated a particular area.

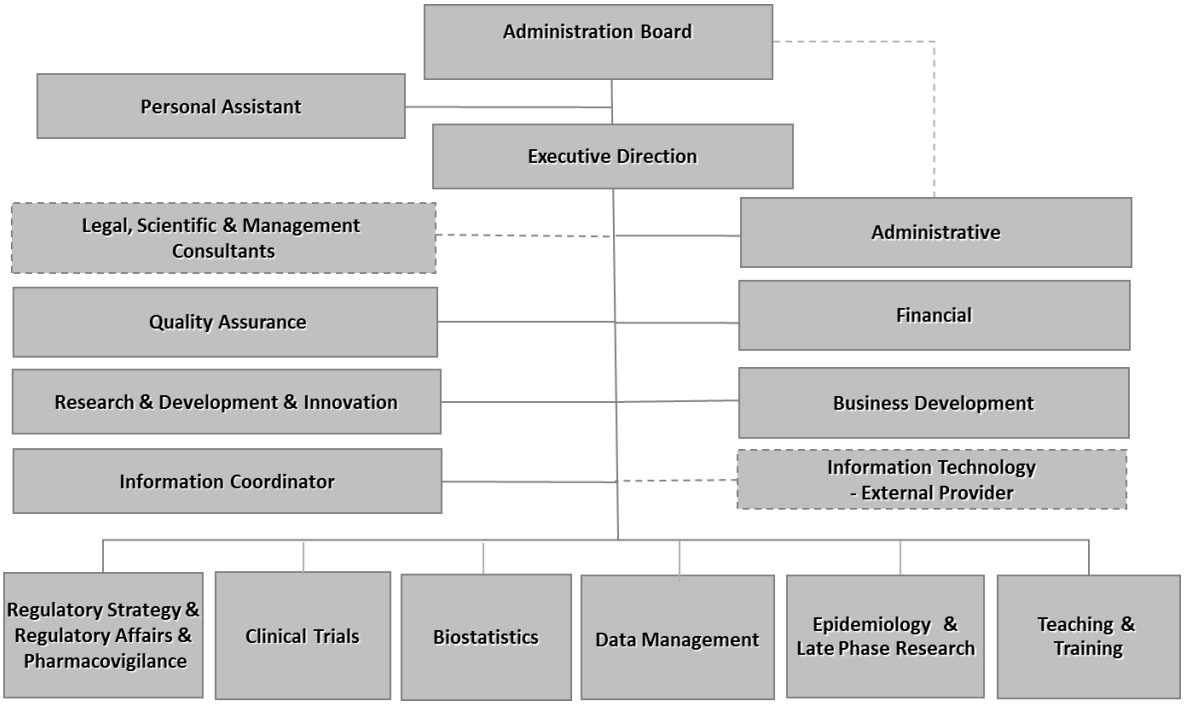

Figure 1 - Organogram of Eurotrials Portugal (adapted from an internal Eurotrials' presentation, 2011)

The main services provided by Eurotrials are research methodology and consulting, study design elaboration, Protocol/ Case Report Form (CRF) development, implementation of clinical trials, project management, and monitoring activities (Phase I, II, III, and IV). It also grants data management and biostatistics, statistical and clinical reporting, epidemiological & late phase research, health economic studies; medical writing; quality assurance auditing and consulting; regulatory affairs; systematic review and meta-analysis; feasibility analysis and teaching and training (1).

My curricular training was developed at Clinical Trials department under the direct supervision of a Clinical Trials Line Manager, Isabel Pinto, and Head of Clinical Trials, Raquel Reis. In Figure 2 it is represented the organization of Clinical Trials department. The Head of Clinical Trials supervises four lines of clinical trials and each line usually has a Clinical Trial (CT) Line Manager, a Project Manager, a Lead Clinical Research Associate (CRA), a CRA, a CRA trainee and a Clinical Trial Assistant (CTA).

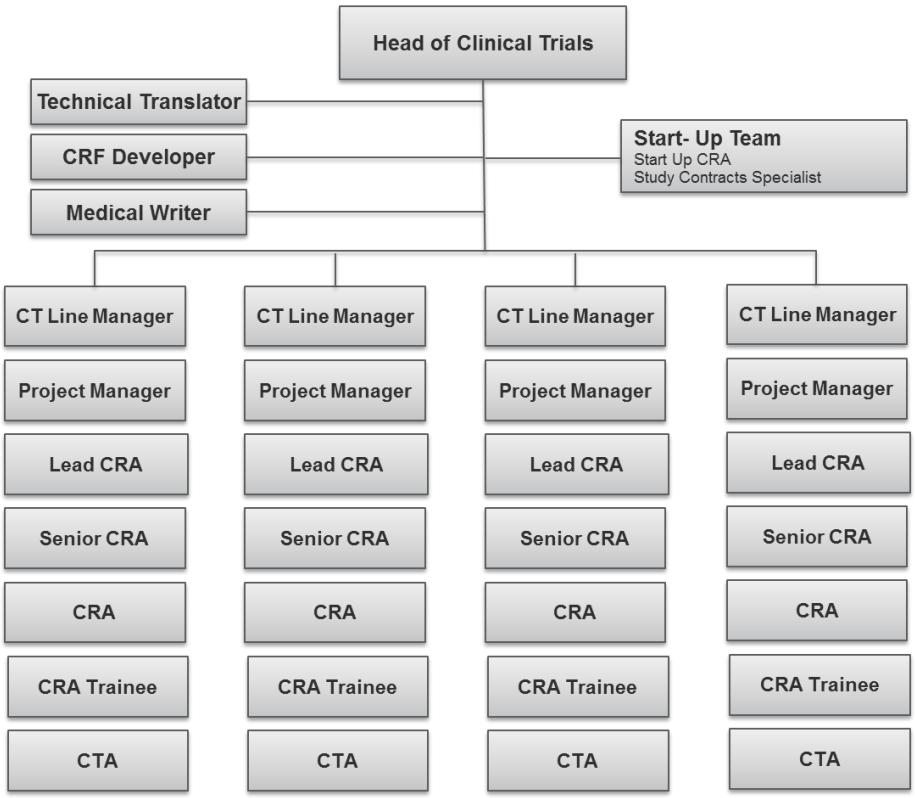

Figure 2 - Organogram of Eurotrials Clinical Trials Department (adapted from an internal Eurotrials' presentation, 2011). CRF – Case Report Form; CRA – Clinical Research Associate; CT – Clinical Trial; CTA – Clinical Trial Assistant.

1.1.2. ROCHE

F. Hoffmann-La Roche Ltd. Is a Swiss global health-care company that operates worldwide. It was founded on 1896 in Basel (Swiss). During the twentieth century the company grew and became a reference in pharmaceutical research, with an active presence in over 150 countries, including Portugal (2).

Roche's operating businesses are organized into two divisions: Pharmaceuticals and Diagnostics. The company also owns the American biotechnology company Genentech and the Japanese biotechnology company Chugai Pharmaceuticals. The Figure 3 represents Roche divisions and subsequent acquisitions (3).

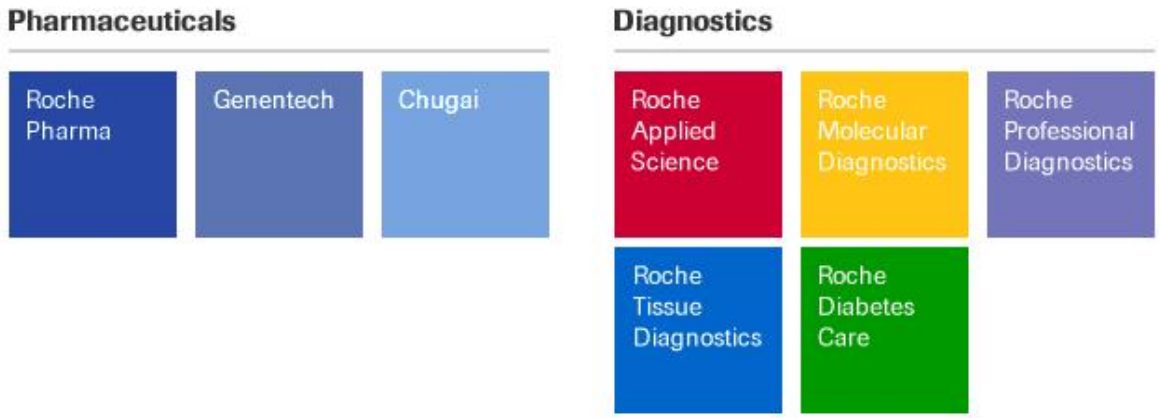

Figure 3 - General Structure of Roche (3)

It is known that today, Roche supplies a wide range of diagnostic instruments and tests for disease detection and monitoring. In the therapeutic area, Roche has brought many effective drugs onto the market in the last few years. The main areas where Roche are focused include oncology, viral infections, metabolic and central nervous system disorders and inflammatory diseases. Oncologic drugs undoubtedly represent the majority of revenue for Roche (3).

In Portugal, Roche started its activities in 1973; currently it has about 300 employees and is organized as presented in Figure 4 – Roche Diagnostics - and Figure 5 – Roche Pharmaceuticals.

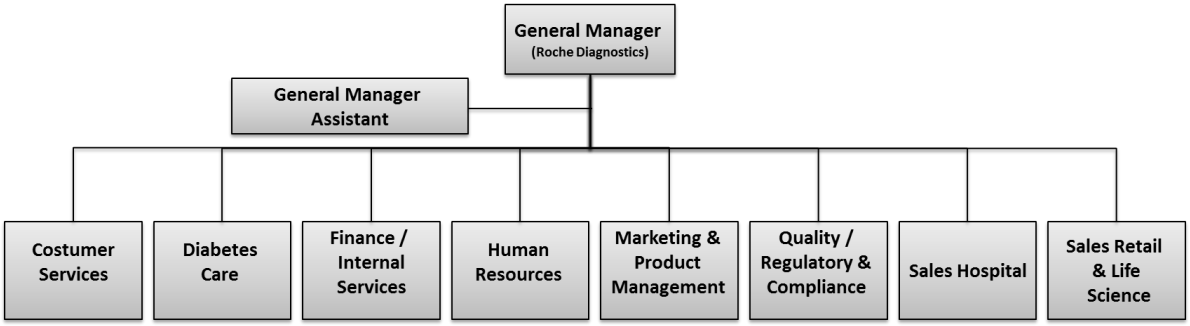

Figure 4 - Organogram of Portugal Roche Diagnostics (adapted from an internal Roche's presentation, 2011)

Roche Diagnostics, present in Portugal through Roche *Sistemas de Diagnósticos, Lda*., currently have 91 employees and operates throughout the country from the Roche offices in Amadora and Rio Tinto. Roche *Sistemas de Diagnósticos, Lda*. Is certified according with ISO 9001:2008 (2).

Roche diagnostic division has an innovative role by cooperating with the Pharmaceutical division in the creation of tools for identifying effective therapies for complex health problems. Its main services are consulting and integrated solutions; clients assistance; commercial and financial services and regulatory affairs (2).

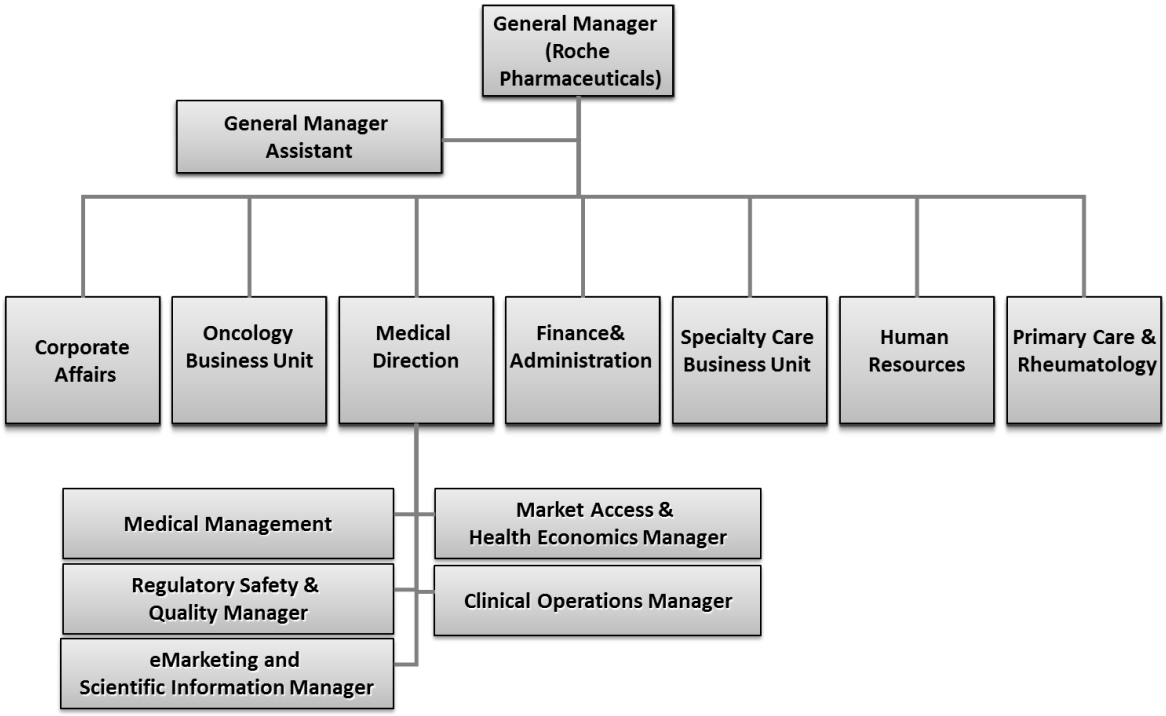

Figure 5 - Organogram of Portugal Roche Pharmaceuticals (adapted from an internal Roche's presentation, 2011)

The pharmaceutical sector, namely Roche Pharmaceuticals, is the largest of the group representing about 60% of total business (2). My curricular training was developed at this division, at Medical Direction department particularly at Clinical Operations under the supervision of the Clinical Operations Manager, Cristina Ventura. In Figure 6 - Organogram of Roche Medical Direction department (adapted from an internal Roche's presentation, 2011)Figure 6 can be seen how Medical Direction department is divided, specifying the organization of the Clinical Operations department where I was included.

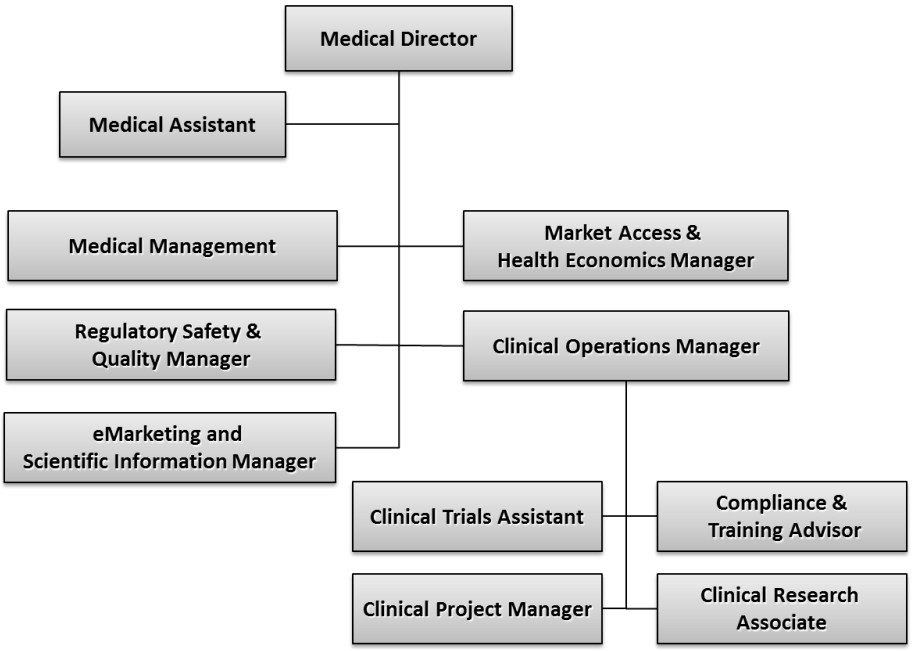

Figure 6 - Organogram of Roche Medical Direction department (adapted from an internal Roche's presentation, 2011)

1.2. STATE OF THE ART

Clinical Research is defined as the research which is performed for patients, with interventions which are relevant to those and whose results are intended to serve as a basis for the diagnose decision, treat or make a prognosis of diseases that affect them (4).

Clinical Trials are the universally accepted method for the investigation. These trials should be par excellence, randomized and controlled, to ensure the scientific validity of results (4). According to International Conference on Harmonisation – Good Clinical Practice (ICH-GCP), Clinical Trials are defined 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).

In addition to clinical trials, the observational epidemiological research is a key component of health research, which allows determining prevalence and incidence of certain diseases in the population, its characterization, quantification of the consumption of health resources, as well as the effectiveness and safety of drugs in the context of current clinical practice (4).

Clinical Research has always been essential to the strategic development of pharmaceutical industry. However, this industry is constantly undergoing a change and it is verified that the concept of developing internally all this process and confine access to information or resources to third parties is becoming obsolete. In fact, in-house resources are getting exhausted with a very thin product pipeline and in addition many drugs are going off patent hampering company sales and increasing competitiveness. Generics market is growing fast and adding this to the low productivity of Research and Development (R&D) process and higher costs for product approval,

these are the major market feature for decreasing pharmaceutical profits. In other hand, global outsourced R&D is increasing every year leading to rise in business prospects for Contract Research and Manufacturing services (6).

Outsourcing is being used more strategically as an ongoing part of a company's overall business strategy. Outsourced activities can be in various fields from the drug discovery until the manufacturing of the products (6).

CROs, defined on ICH-GCP as a person or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions, first showed up in the biotech industry in the late 1970s and quickly took on a significant role in R&D, after expanding from drug discovery and preclinical work to clinical trials, drug manufacturing and even marketing (7).

Outsourcing allows pharmaceutical companies to ramp up the R&D operations at a fast pace with minimal capital outlay. Some of the benefits of outsourcing are the reduction of overall costs; improvement of net earnings and cash flow; diversion of resources to focus on other skills such as marketing and minimization of investments in capital-intensive facilities (6).

Currently, pharmaceutical companies and outsource partners work in symbiotic relationship where pharmaceutical companies provide their core competencies in marketing and commercialization and outsource partners supply new innovative products. To maintain this symbiotic relationship the outsourcing partners need to confidentially retain the proprietary knowledge and meet the regulatory compliance (6).

Regardless of outsourcing agreements between pharmaceutical industry and CROs, clinical research always involves multiple sources of specific expertise from diverse areas, such as research and development, technical consulting, administrative and regulatory.

As represented in Figure 7, there is a long and well defined process between the discovery of some molecules with essential characteristics to be a drug and the new drug ready to be on the market. This process may take 10 to 15 years and is divided in six main steps: 1) Laboratorial tests; 2) Pre-clinical tests; 3) Clinical trials; 4) Authorities submission; 5) Approval and 6) Registry and Marketing (8).

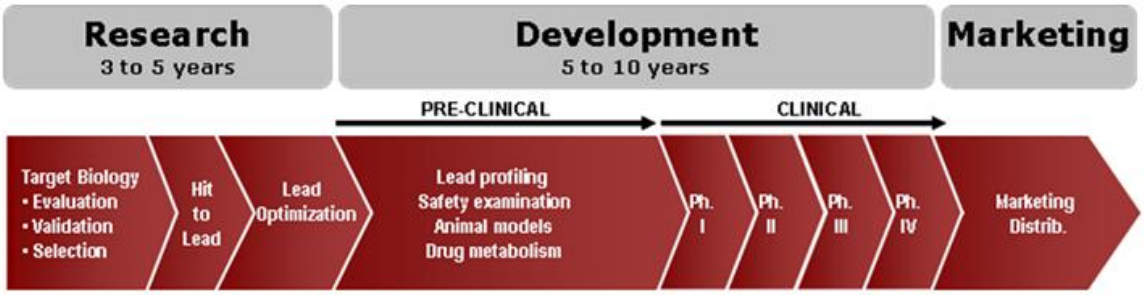

Figure 7 - Process of drug development, including estimated timelines (1)

The first step involves the identification of potential therapeutic targets resulting from research or medical needs unfilled. Numerous molecules are generated starting from chemical molecules manufactured and based on physic-chemical properties and pharmacological profiles desirable. These molecules will be evaluated for their ability to produce the desired effect *in vitro* and usually only a very small number of molecules reach the next stage which involves animal experimentation (pre-clinical studies). Extrapolation of the results obtained of pre-clinical studies in absence of evidence of potential toxicity allows exploratory tests phase and the first exposure in humans through clinical trials. These are carefully designed, conducted and controlled in accordance with consensual protocols to ensure compliance with high standards of safety, patient treatment, quality and interpretation of data (9).

Clinical trials have evolved towards the harmonization of procedures, focusing on patient safety, with the consent of all participants - a common denominator in any trial. Currently, ethical issues and inherent risks in a clinical trial, as well as its impact on patients involved, are important issues that are carefully evaluated. This regulation was established based on documents as the Nuremberg Code and Helsinki Declaration which form the safety and ethical of participation of individuals in clinical trials. Nuremberg Code was developed on 1947 and establishes ten basic principles to protect participants in clinical trials (10). Helsinki Declaration was developed on 1964 in order to establish ethical codes to physicians and to protect the clinical trials participants worldwide (11). ICH was created in 1990 in order to avoid existent differences on requirements to the drug development on the three pharmaceutical global markets: European Union, Japan and United States (12). On 1996 ICH-GCP guidelines were accepted in these three markets and it became the guideline to be followed on the development and conduction of clinical trials (13). Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) was developed on 2000 and became the standard dossier used on Europe, Japan and United States to submit collected data from clinical trials to the applicable governmental authorities (14). On May 2004, Directive 2001/20/EC became one legal document in the 25 member state of the European Community. This document establishes new requirements to the investigator and his clinical investigational teams to conduct non-commercial trials (15).

Currently, Clinical Research in Portugal is regulated by Law 46/2004 of 19th August (transposed into National Law of Directive No 2001/20/EC of the parliament and Council of 4th April) (16) and Decree-Law No. 102/2007 of 2nd April (17), which together establish the legal regimen for the conduct of clinical trials with medicines for human use in Portugal. In addition, conducting a clinical trial depends on the approval/ prior opinion of three independent entities: National Authority of Medicines and Health Products (INFARMED); Ethics Committee for Clinical Research (CEIC) and National Committee for Data Protection (CNPD); and also on the Administration Boards approval of clinical trial contract (18).

1.3. TRAINING OBJECTIVES

The initial training plan included a cross-disciplinary experience that would allow passage through the various company departments, and a mono-disciplinary experience that would involve specialized preferred work. However, despite of being part of a curricular training process I was treated and recognized as belonging to a work team with responsibilities and duties equivalent to any independent training CRA. Additionally to my experience in Clinical Trials Department (the chosen option for the mono-disciplinary experience), I was also able to go through Biostatistics and Data Management departments (cross-disciplinary experience).

The main goals established for my curricular training were:

- To understand the communication flow and inherent work in Clinical Trials department;
- Understand how to organize the monitoring activity both from the point of view of a CRO as a Pharmaceutical Industry;
- To be able to practice autonomously and efficiently the involved procedures in CT monitoring.

The secondary goals were:

- Meet the host companies, the other departments and the various activity ranges;
- To apply theoretical knowledge acquired in the Biomedical Sciences degree and in the master's course in Pharmaceutical Biomedicine, enabling a smooth relationship between the output of education and training systems and the contact with real work world;
- Attend courses/ trainings that allow me to acquire new knowledge important to my professional practice;
- Train the writing of technical documents;
- To complement and enhance social and professional skills by attending training in a real work context;
- Develop critical thinking in concrete situations in the clinical research area.

2. ON-THE-JOB TRAINING

2.1. GENERIC TRAINING

Once in Eurotrials, the opportunity to pass for some departments in order to understand how they work and interact with the other departments was given to me. The learned knowledge in the department of Data Management and Biostatistics will be described in the two following sections.

2.1.1. DATA MANAGEMENT

During my curricular training I had the opportunity to spend one day to understand how Data Management Department works, how the information flow is made and the interactions between this department and the others during all process of clinical research. Since it was only possible to spend one day in this Unit, it was decided to have theoretical approach about general procedures in order to acquire essential information to develop the activities as a CRA.

For this, I could understand that this department in Eurotrials uses cutting-edge technology in electronic data collection and a validated data management system which is in strict compliance with FDA 21 CRF part 11. The new data-collection technologies include Web portals (to manage each project's data), ePRO (electronic Patient Reported Outcomes, such as digital patient diaries by mobile phone or PDA, diagnostic and measuring devices with electronic data collection), Interactive Voice Response System (IVRS) and Interactive Web Response System (IWRS).

In this department the Head of Data Management supervises the Senior Data Manager and has the collaboration of the Data Manager Quality Controller, Medical Reviewer and Case Report Form Developer. The Senior Data Manager in turns usually supervises Data Managers, Database Operators, Data Entry Operators and Information Technology Analyst and Developer.

This department has participated in a large diversity of projects distributed for multiple areas, namely, Pneumology, Psychiatry, Vascular, Stomatology, Rheumatology, Nephrology, Medical Hydrological, Cardiology, Surgery, Endocrinology, Infections Diseases, Neurology, Oncology, Otorhinolaringology and others (Figure 8).

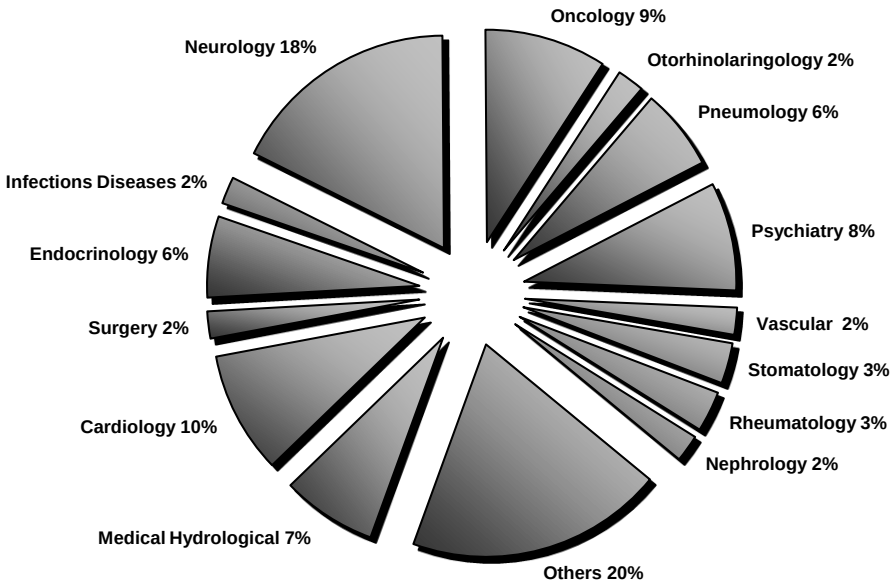

Figure 8 – Percentage of projects per scientific areas where Eutrotrials Data Management Department was involved until May 2011 (adapted from an internal Eurotrials' presentation, 2011).

Data Management is an essential element throughout a clinical trial. It can accompany the study from the beginning - CRF development - to the end - database standardization.

Throughout the study there are two essential documents used as maintenance releases work: Protocol and CRF (either developed internally or not).

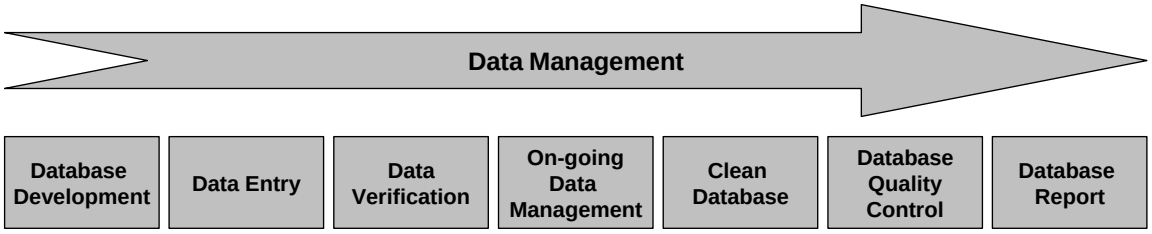

Figure 9 - Information Flow in Eurotrials Data Management Department

The information flow in Eurotrials data management begins with the Database Development (as seen in Figure 9). However, sometimes the Data Management Department is contracted to develop CRF. In these cases, the CRF development precedes the database development.

For a successful CRF development is very important to understand how the data will be collected and assure that parameters of the CRF are in compliance with study protocol. After being drawn up, it is sent to statistical department where it will be revised to ensure that all the required fields are present and in compliance with protocol.

After this, timelines are defined and the first document of the process is elaborated: Data Management Plan. This document includes important and formal information about how to handle data both during the research and after the project is completed, such as CRF completion guidelines, CRF tracking instructions, data entry guidelines, the data querying process and how corrections will be made. The goal of a Data Management Plan is to consider the many aspects of data management, data preservation, and analysis before the projects begins; this ensures that data are well managed in the present, and prepared for preservation in the future (19).

Annotated CRF is the second important document to be elaborated even before the beginning of clinical trial. An annotated CRF is a CRF in which the variable names are written next to the fields provided for the investigator. It serves as a link between the database/data sets and the questions on the CRF. The goal of Annotated CRF is to help both the programmer and the reviewer to understand the data sets since it defines variables, tables and how the fields will be noted. Thus, it is used from data entry step until the statistician (19).

There is another document which has the same goal of Annotated CRF: Data Definition Documentation. This document consists of a Table of Contents and a collection of data description tables. The table of contents lists out all the data included in a submission and provides the location and information on each data domain. The data description tables describe the attributes and origins or derivation of all variables in each data domain. Basically, it is a technical print-out which is on Trial Master File of every study. However, it is not widely used by data managers due to its size (making it impractical) (20).

The elaboration of these documents corresponds to the two first steps of database development – Planning and Requirements Gathering. After planning phase, the fields must be defined and tables created (Conceptual Design). Then it is necessary to create the logical design of application and database converted then to software systems that will be used to implement the database (Logical & Physical Design). Programming units are promoted to the system test environment, where the entire application and database is assembled and tested (Construction and Challenge). A functional report is generated by Quality controller and the Data Manager is responsible for correcting the findings. After the correction, database is approved by two team workers and is ready to receive data. Database Support Documentation is generated in the final of this process for each study and it is useful to train data entries.

Commonly used methods to perform data entry are: “single key entry”, “double key entry” and “independent double key entry”. On a “single key entry” system, one person enters the data and another person print the results and compare with source documents. On a “double key entry” one person enters the data and another person enters the same data into a mirror screen and the system compares the values in real-time. In this case, discrepancies are identified in the second they happen and they can be identified and if possible corrected immediately. The method of “Independent double key entry” is similar to “double key entry” with an exception regarding the second entry which is independently done and a program runs later to compare the two sets of entries.

Data are entered and cleaned throughout the study. However, data quality activities must be conducted in order to eliminate potential errors that may distort the statistical analysis. To avoid this, all queries must be generated and resolved, and Data Validation Plan must be executed. Data Validation Plan defines what is made manually or on an automatic way. Currently in 90% of cases this validation is automatic, that is, there is software which is programmed to cross the

parameters which have to be crossed. In the other 10%, the data managers have to found manually discrepancies between the fields.

After data validation, when a discrepancy is found, it is sent to solve for investigational sites. Sites have to solve within a limited period of time and so long as the discrepancy exist it will again be sent to site to be resolved. Data validation occurs only after discrepancy resolution. If discrepancy remains unresolved and there is no time to send more discrepancies to site, data manager has to report deviations and has to catalog the errors (with sponsor indication) in order to alert statistician to exclude data from deviations.

When all issues are resolved, sponsor gives authorization to consider database "released" for analysis, i.e., locked. Data Set is send to statisticians and to provide a stable dataset for analysis, the database should not be changed after release, except in extreme cases and with sponsor authorization.

In addition with dataset, randomization codes are sent to statistician in order to reveal which patients were on what treatment. This allows comparative analysis by treatment.

The final step of data management process on the study culminates with Data Management Report which includes descriptive information about the study such as, number of patients who discontinued; screening failures and Adverse Events (AE) occurred.

2.1.2. BIOSTATISTICS

As happened in Data Management department, since it was only possible to spend one day in this unit, I should have theoretical approach about general procedures in order to acquire essential information to develop the activities as a CRA.

The biostatistics department provides a wide range of services adapted to the needs of each project such as statistical advice and consultancy, study reports and assistance in preparing articles for biomedical journals.

It also ensures correct methodological development and appropriate planning in clinical trials and guarantees the quality of protocols and reliable data processing, all of which are crucial to the success of any research project (1). This department has already a large experience on projects in many areas of clinical research as represented on chart below.

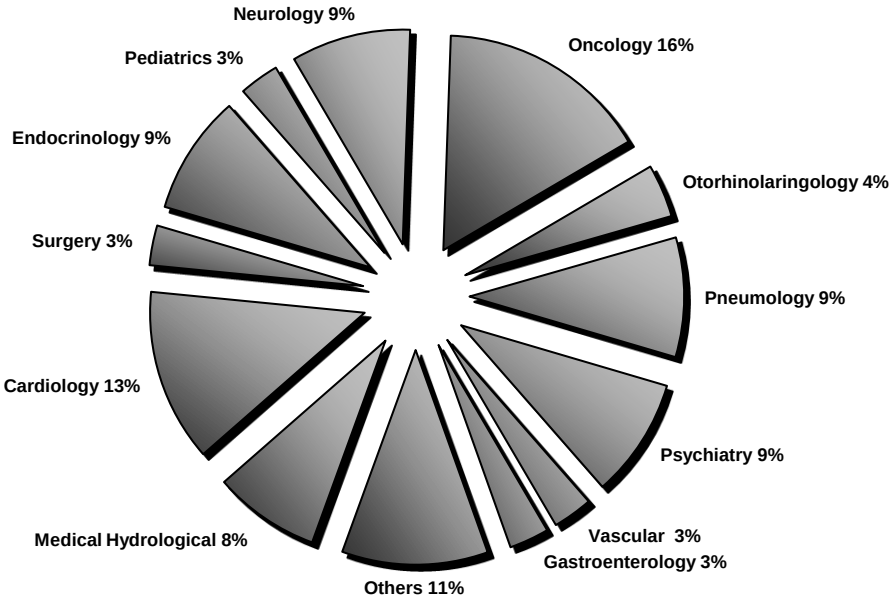

Figure 10 - Percentage of projects per scientific areas where Eutrotrials Biostatistics Department was involved until May 2011 (adapted from an internal Eurotrials' presentation, 2011).

Currently this department is constituted by a five elements team, namely, Head of Biostatistics, Senior Statistician, Senior Consultant, Statistician and Statistician Trainee.

Biostatistics department collaborates with all departments in Eurotrials. In Figure 11 I have summarized the connections between biostatistics department and the other departments of Eurotrials; in particular, I would like to emphasize the link between this department and the department where I developed the specific training.

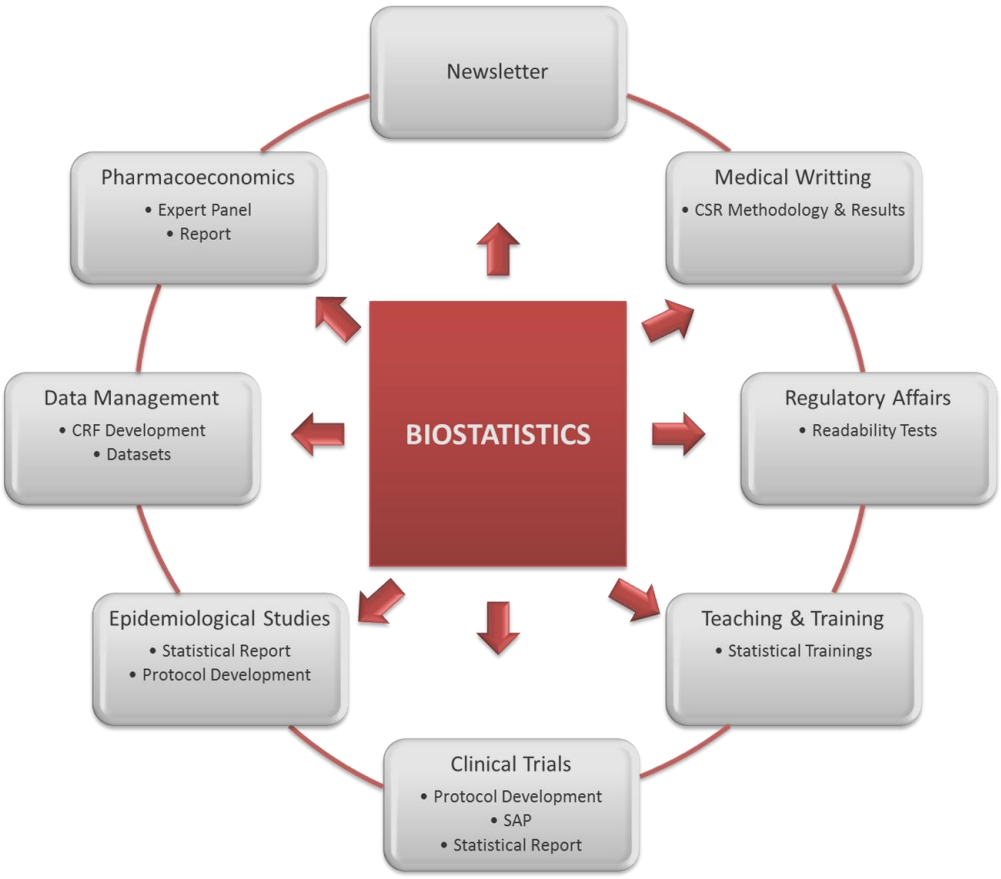

Figure 11 - Biostatistics Department Interactions with other Eurotrials' departments (adapted from an internal Eurotrials' presentation, 2011).

Biostatisticians have an important role in the protocol development once they elaborate the methodology. They also create randomization lists and Statistical Analysis Plan (SAP). This plan is a critical link between the conduct of the clinical trial and the Clinical Study Report (CSR). It defines the statistical analysis that will be performed for the clinical trial and all of the Statistical Analysis System (SAS) output required to be included in the CSR. After data managers' handover datasets to biostatistics department, as mentioned on the previous topic, biostatisticians have the responsibility to analyze the data and then to perform the statistical report.

In the epidemiological studies there is no obligation to perform the SAP. Thus, in these studies the biostatistician performs a report only with a detailed statistical methodology.

Biostatisticians have also an important role on the pharmacoeconomic studies which compares the value of one pharmaceutical drug or drug therapy to another. A pharmacoeconomic study evaluates the cost and effects of a pharmaceutical product.

In most clinical trials, economic data are not collected throughout the study. Even when they are, the data may need to be projected to populations, time periods, or settings that were not observed in the clinical study. In these cases, decision-analytic models may be used to generate some of the missing information. The data in a health economic model may be derived from various sources and is associated with varying degrees of uncertainty. Potential sources for the input variables in a model are clinical trials, literature, medical records, databases, expert panels, and official costs lists for resource utilization (21).

When a pharmacoeconomic study comes to biostatistics Eurotrials department if there is any defined method to perform the study, this is the first thing that biostatistician has to do. After this, a literature revision is made and a model is crated or reviewed, as applicable. Then, a questionnaire is made and an expert panel is selected to achieve a consensus. The expert panel is constituted by 5-7 physicians of the therapeutic area involved in the study and chosen by the sponsor. They cannot be from the same region or the same hospital from each other. There are 3 methods to constitute an expert panel (22, 23): Delbecq method; Delphi method; and Key-Informers method. The first one involves a face to face meeting with all experts, where the questionnaire parameters are discussed until reaching a consensus. The second one consists in sending the questionnaires by courier; the experts answer and send back to statisticians. A consensus questionnaire is made and sent again to experts to their approval. The last one consists on a personal interview to each expert (key-informer) in order to understand the different opinions about the subject in question. After all interviews made, a consensus questionnaire is made and sent to experts to their approval. Delbecq method is the most widely used because the estimates obtained by face to face consensus are more robust. After the expert judgment, costs calculation is made and inserted in the model. Then, the model is tested and a report is elaborated.

Biostatisticians usually collaborate also with Regulatory Affairs department in the readability tests. These tests have as a fundamental goal to understand if patient information leaflet is on an accessible language and are easily understandable to the population in general.

2.1.3. General Training

Throughout the curricular training I had the opportunity to attend various trainings that contributed to my professional development.

I had to learn Standard Operating Procedures (SOP) both in ET and Roche. Additionally I had the opportunity to attend the following trainings:

- "Observational research: the view of different stakeholders and the practical experience of conducting observational research", by Maria João Salgado from Eurotrials, one hour training;
- "Clinical research networks, are they in tune with sponsor's needs?", by Ana Filipa Bernardo from Eurotrials, one hour training;
- "Planning and structuring investigational protocols", by Luís Veloso from Eurotrials, one hour training;
- "Time management", by Graça Silveira from Eurotrials, one hour training;
- "Study coordination in investigational site", by Susana Bule from Eurotrials, five hours training;
- "(In) security of information", by Pedro Galvão from IBM, three hours training;
- "Breast cancer", by Hermínia Pereira from Roche, four hours training;

- "Breast cancer – from diagnostics to treatment", by Ida Negreiros from Roche, four hours training.

All these trainings were very useful in that they facilitated the integration of important information used in the everyday practice and, in some cases, these helped to acquire more information about therapeutic area of projects in which I was involved.

2.2. SPECIFIC TRAINING: CLINICAL TRIALS MONITORING

Most of my training was spent in clinical trials monitoring, initially at Eurotrials and then, at Roche.

According to ICH-GCP, monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOP, GCP, and the applicable regulatory requirement(s) (5).

Trial monitoring intends to guarantee that the rights and well-being of human subjects are protected and that the reported trial data are accurate, complete, and verifiable from source documents (5).

CRAs should be appointed by the sponsor, should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. These qualifications should be documented. Despite this, CRAs should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (5).

Clinical trials monitoring requires that CRA in accordance with sponsor' requirements, ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and trial site:

1. Acting as the main line of communication between the sponsor and the investigator;

2. Verifying that the investigator has adequate qualifications and resources, that facilities are adequate to safety and properly conduct the trial and remain adequate throughout the trial period;

3. Verifying, for the investigational product, the storage times and conditions, the eligibility of patients to receive the investigational product, that information regarding properly using, handling, storing and returning were provided, controlled and documented and that the disposition of unused investigational product at the trial sites complies with applicable regulatory requirements and is in accordance with sponsor;

4. Verifying that the investigator are adequately informed about the trial and follows the approved protocol and all approved amendment, if any; that written informed consent was obtained before each subject's participation in the trial and that investigational staff team are performing the specified trial functions and have not delegated these to unauthorized individuals;

5. Ensuring that investigator receive current Investigator's Brochure, all essential document and trial supplies needed to conduct the trial properly;

6. Verifying that the investigator is enrolling only eligible subjects and reporting the subject recruitment rate;

7. Verifying the trial documentation, such as source documents, required submissions, applications, reports and CRFs, are accurate, complete, legible, dated and maintained;

8. Determining if all adverse events are appropriately reported within the time periods required by GCP, the protocol, INFARMED, CEIC, the sponsor, and the applicable regulatory requirement (s).

The CRA plays a major role in the successful conduct of a trial. Quality and trial results are directly influenced by CRA capabilities and the established relationship with investigator and study tem. The CRA must perform comprehensive site management and monitoring activities which include the following types of monitoring visits:

1. Pre-study qualification visits (after the feasibility);

2. Initiation visits;

3. Interim monitoring visits;

4. Close-out visits.

All these activities must be performed in accordance with ICH-GCP (5) to ensure all investigational sites are compliant with applicable regulations and protocol requirements. The main CRA objective is to ensure timely subjects recruitment, patient rights, safety and data integrity. However, these tasks should be always accompanied with site management documentation and follow-up activities to ensure that site staff remains motivated and focused. Sometimes this motivation will falter over study, especially in long-term studies, which were going through several CRAs and constant changes in study team. In these cases is necessary a greater effort in order to motivate the team and ensure that they continue to enhance the study and its importance.

In general, CRA should be able to balance characteristics as sensitivity, diplomacy, flexibility and kindness with firmness and precision to manage conflicts.

Throughout my experience in clinical trials department I was given the opportunity to accompany experienced CRAs and to understand these mentioned aspects of being a CRA as well as the opportunity to perform almost all planned activities with the exception of study implementation activities and audits/inspections preparation tasks, due to the fact that during my training none of the studies where I was involved were in these two phases. Along the training I was able to perform activities in different studies and in different phases of clinical trial cycle, as represented in Table 1.

CT REF. NO.	CLINICAL TRIAL DESCRIPTION	ACTIVITY DEVELOPED
1	Randomised three-arm multi-centre comparison of 1 year and 2 years of a treatment versus no treatment study in women with HER2-positive primary breast cancer who have completed adjuvant chemotherapy.	**Monitoring**
2	A single arm, multi-centre, international, continuation trial of a recombinant humanized antibody study in patients with HER2 overexpressing tumors.	**Monitoring**
3	An open-Label randomized phase III study in patients who have undergone surgery for colon carcinoma, AJCC/UICC Stage III (Dukes Stage C).	**Close-Out**
4	Multicenter, double-blind, randomized, placebo-controlled, parallel group, prospective, event driven phase IV study on Pulmonary Arterial Hypertension.	**Monitoring**
5	Open-label, Uncontrolled, multicenter, Phase II study in patients with metastatic colorectal cancer.	**Monitoring**
6	Open, Randomized, Phase IV, multicenter Clinical Investigation in patients with Mild to Moderately Active Steroid Dependent Ulcerative Colitis.	**Monitoring**
7	Open-label, randomized, controlled, multicenter phase III study for subjects with advanced gastric adenocarcinoma of the gastro-esophageal junction.	**Monitoring**
8	Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial in subjects with a first clinical event at high risk of converting to Multiple Sclerosis.	**Monitoring**
9	A 2 year randomized, single-masked, multicenter, controlled phase IIIb trial in patients with macular edema and visual impairment secondary to Diabetes Mellitus.	**Initiation**
10	Phase III randomized trial to evaluate the efficacy and safety of second-line therapy in patients with B-Cell Chronic Lymphocytic Leukemia.	**Monitoring**
11	Multicenter, randomised, double-blind, Phase III trial to investigate the efficacy and safety of therapy in patients with stage IIIB/IV or recurrent non-small cell lung cancer after failure of first line chemotherapy.	**Monitoring**
12	A multicenter, phase III randomized, double-blind, 3-Arm, placebo-controlled, 78-week parallel group study to assess the efficacy and safety of the therapy in subjects with Mild to Moderate Alzheimer's Disease.	**Feasibility**

Table 1 – Description of Clinical Trials and activities where I was involved during my curricular training

Having worked in various life stages of a clinical trial allowed me to understand the differences that each of these phases involve at time spent and type of work developed by CRA. In Table 2 there is a schedule of activities developed in my specific training, accordingly with the main phases of the life cycle of CT.

Developed Activities during the Training												
		2010				2011						
ACTIVITIES		SEP	OUT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL
Study Specific Documents Familiarization	Protocol	X	X	X	X	X			X	X		
	Informed Consent Form	X							X	X		
	Case Report Form	X			X				X	X	X	X
	ICH/Legislation/SOPs	X	X	X			X		X			
Feasibility	Feasibility Contacts					X	X	X	X			
	Feasibility Visits											
	Feasibility Status to Sponsor					X	X	X	X			
Study Implementation	Pre-study Visits (Preparation, execution and report)											
	Site Contracts preparation											
	Submission to CNPD, CEIC and INFARMED											
Study Initiation	Investigator and Pharmacy Files					X	X	X				
	Trial Master File (Central File Archiving & Maintenance)											
	Initiation Visit (Preparation, execution and report)			X		X		X				
Study Monitoring	Investigator and Pharmacy Files (Archiving and Maintenance)						X	X	X	X	X	X
	Trial Master File (Central File Archiving & Maintenance)	X	X	X	X	X	X	X	X	X	X	X
	Safety Information Notification (AEs/ ASR/SUSARs)								X	X	X	X
	Newsletters											X
	Monitoring Visits		X		X			X	X	X	X	X
	In-house Monitoring (communication with Sponsor and sites, status reports, CRF revision and, management of queries, drug, supplies and documents, reports, follow-up letters and laboratory procedures)	X	X	X	X	X	X	X	X	X	X	X
	Study documents translation		X			X	X					
	Drug accountability		X					X	X			X
	Amendment Notification (CEIC, Principal Investigator)	X										
	Substantial Amendement Submission											
	Study Payments to sites	X										
	Audit (Preparation, execution and follow-up)					X						
Study Close-Out	Study Close-OutInvestigator and Pharmacy Files (Archiving and Maintenance)										X	X
	Trial Master File (Central File Archiving & Maintenance)										X	X
	Close-out Visit (Preparation, execution and report)										X	X
	Data Management and Database Close-out											
	Statistical Analysis											
	Clinical Study Report											

Table 2 - Schedule of activities during my curricular training

I will now describe in more detail the planed and undertaken activities during my experience as CRA. I will focus more on the practical activity part since this experience had as main goal the consolidation of already acquired theoretical knowledge from masters' degree. In Table 3 for the 12 CTs where I was involved there is a description of therapeutic area, phase, type of randomization, blindness and comparator.

CT Ref. No.	Therapeutic Area	Phase	Randomized	Blind	Comparator
1	**Oncology** (Breast Cancer)	III	√	Open Label	√
2	**Oncology** (HER2 overexpressing tumors)	IV	Single arm	Open Label	Uncontrolled
3	**Oncology** (Colon Carcinoma)	III	√	Open Label	√
4	**Cardiology** (Pulmonary Arterial Hypertension)	IV	√	Double-blind	Placebo-controlled
5	**Oncology** (Colorectal Cancer)	II	√	Open Label	Uncontrolled
6	**Gastroenterology** (Ulcerative Colitis)	IV	√	Open Label	√
7	**Oncology** (Gastric adenocarcinoma)	III	√	Open Label	√
8	**Neurology** (Multiple Sclerosis)	III	√	Double-blind	Placebo-controlled
9	**Ophthalmology** (Macular Edema and Visual Impairment secondary to Diabetes Mellitus)	IIIb	√	Single-Masked	√
10	**Haematology** (B-Cell Chronic Lymphocytic Leukaemia)	III	√	Double-blind	√
11	**Oncology** (Non-Small Cell Lung Cancer)	III	√	Double-blind	√
12	**Neurology** (Mild to Moderate Alzheimer's Disease)	III	√	Double-blind	Placebo-controlled

Table 3 - Characterization of CTs where I was involved, including therapeutic area, type and study phase. All trials were international and multicentric.

The first phase of my experiment as CRA began with the reading and the acquisition/consolidation of theoretical knowledge from specific trainings, SOPs, guidelines, directives and laws applicable to the specific tasks inherent to CRA role. This initial reading was guided by Susana Bule in order to clarify possible doubts and assure that this knowledge was understood.

In this phase, I realized that when CRA worked in a CRO, despite having to know the SOPs of the company, also have to learn about each client's specific SOPs. CRA can use internal SOPs, external SOPs or both, depending of each project and accordingly with established contract.

2.2.1. FEASIBILITY

In the course of my training there was the opportunity to do a feasibility study assessment in a neurology study. A properly designed and executed feasibility study can provide an overview of a clinical trial's challenges and the strategies to eliminate risks before the study begins.

My experience with feasibility process began when a list of possible sites was given to me. Accordingly with previous information and past experience, sponsor had already chosen some sites to study development in Portugal and sent a list of them to CRO. My first task was to complete that list with other potentially interested sites and correct some mistakes regarding sites that were already on the list. Then, after sponsor approval, sites were contacted in order to receive the first information about the study and to understand if investigators were interested in participate in the feasibility study assessment. During this phase establishing contact with investigator was not always easy and in some cases, it was impossible due to their unavailability or even their lack of interest. Beyond this, the same investigators accepted to participate in the trial and in these cases, were asked to sign a confidential agreement and to answer a questionnaire sent by e-mail from international team. During this process, several status information were sent between CRA and international team until all potential interested investigators answered the questionnaire and send it via e-mail.

All this process seems easy. However, if we take into account the short timelines provided by the sponsors, the unavailability of investigators and hence the need to repeat the demand for answering online the questionnaire online, it is not always an easy and quick process. Beyond this, as this process is done online directly via international team to investigators, the CRA had a more passive role to play. However, it is the CRA who knows perfectly if sites usually are engaged with study tasks, if investigators usually demonstrate commitment and willingness to participate in the study and if sites have the real interest in participate in clinical trials. This often means that feasibilities are a very challenging part of a Clinical Trial. In this process it is already crucial to identify potential interested sites of non-interested sites.

2.2.2. INITIATION VISIT

During my training I was given the opportunity to prepare and accompany all initiation visits with an experienced CRA. These were carried out in a study that involved patients with macular edema and visual impairment secondary to diabetes mellitus.

The main goal of this phase is to remember the procedures, criteria and design of the study. Ideally, at this time the study team has already an idea about the study and knows what procedures must be followed (24). However, in practice not always is like that and some teams have no idea about criteria or specific procedures of the study. In any case, after this visit study team and site must be prepared to include the first patient in the study. CRA has a crucial role at

this point, being responsible for training and clarifying all doubts as well as to promote immersion in the study, intercommunication and mutual help between all members of site study team (24).

Before initiation visit, it is always necessary to obtain all essential documents (also known as green-light documents), such as INFARMED authorization, CEIC and National Data Protection Authority approval, site Administration Board approval and signed Financial Agreement, ethics approval of National Coordinator and Investigators *Curriculum Vitae*. Depending of clinical trial type and sponsor procedures, there may be other documents that are required before the initiation visit.

Even before the initiation visit, CRA confirmed the initiation visit with Principal Investigator (PI) and all study team in advance and sent a written initiation visit confirmation letter with agenda meeting. It is very important that this agenda contain a duration estimate of each topic to be discussed in order to allow study team to organize their work accordingly. Sometimes it is not possible to gather the whole team at the same time. In these cases, CRA has to do separate trainings according with the availability of each onsite team member.

The preparation of the visit has included the following tasks:

- All necessary documents and approvals to initiate the study were reviewed and it was confirmed that no document was missing;
- All essential documents were prepared to take to site, namely last approved version of the protocol and amendments (if applicable) and Informed Consent Form, patient diaries, Serious Adverse Event (SAE) forms; Investigator Site File (ISF) and Pharmacy File (PhF) and other specific study material;
- Presentation was prepared and reviewed as well as all material required for the presentation;
- All documents and forms have to be properly filled at this time, such as, authorization log, site initiation visit log, acknowledgments of receipt of material delivered in site initiation visit and training records, were prepared.

During the visit, I was given the opportunity to present one part of the required information of the study and together with the CRA who accompanied me, the following study information was reviewed and discussed:

- GCP and study objectives;
- Investigational Products information;
- The protocol and all important details such as inclusion/exclusion criteria, study design procedures, timelines, recruitment and protocol violations;
- Case Report Form;

- Informed Consent Form (ICF), AEs, laboratory and pharmacy procedures;
- ISF and PhF contents.

It is very important to guarantee that all doubts about study objectives and design, inclusion/exclusion criteria, informed consent form obtaining and adverse event report are resolved to everyone in the study team. In order to overpass problems of misunderstanding, CRA led to site other support documents as a separately and practical sheet with inclusion and exclusion criteria.

In this study, I was fortunate to be able to participate in all initiation visits which occurred in several sites. With this, I have noticed that every site is different from another and that the CRA has to be flexible enough to adapt to all teams and situations that are so different from each other. In some sites was possible to meet with all study team and in this case there was no need to go to other department to do a separately training. In other sites, the presentation session was initially to investigators and study coordinator and on a day after it was to pharmacists. Sometimes, in these cases, the pharmacists and the investigators did not know each other and this can be a problem in the sense that in situations of medication non-compliance, information could not come easily to the investigator. So depending of the different sites CRA approach and following support to study implementation must be adapted so consistency may exist in every sites despite the sites variable “scenarios”.

After the visit, CRA completed the site initiation visit report which describes how the visit took place, participants, performed procedures, the issues raised by the study team and the actions taken or actions that should be made while following this visit. Currently, the report is made online directly in a sponsor platform. A follow-up letter was also sent to site in order to document all tasks and activities performed in the visit, pending actions and timelines for recruitment.

2.2.3. MONITORING VISIT

During my curricular training it was given me also the opportunity to accompany several monitoring visits in different clinical trials. Despite differences between the therapeutic areas, there are similarities in the preparation, on-site and post-visit procedures.

The main objective of a monitoring visit is to oversee the progress of the clinical trial, ensuring that is conducted, recorded and reported in accordance with the protocol, SOPs, GCPs and applicable regulatory requirements.

In general, there is a Clinical Monitoring Plan defined by the sponsor or project manager of the study which determines specific requirements and activities associated with the study, protocol and sponsor. This plan is very useful once it gives guidance regarding protocol and CRF interpretation, rules to fill CRF, number and interval of planned visits, importance level given to required activities developed in the monitoring visit, study procedures, study team contacts, guidance to know what should be reported and when. CRA organize the study work and site monitoring visits based on this plan.

To prepare the site monitoring visits I had to follow some procedures which are transversal to all studies and that I am going to describe below:

- Schedule a visit with the investigator and site study team. This schedule usually involves a phone call to understand the investigator and site study team availability and then, a letter or e-mail (depending of the study and study site team) should be sent with information on the issues to be addressed, the staff that is expected to attend and the time needed to conduct the on-site monitoring activities;
- Review monitoring reports and follow-up letters from previous visits and other documents such as, correspondence with the site and phone contact reports, in order to check any missing documents, outstanding action, issues and queries that need to be addressed during the visit;
- Send the written confirmation (usually by e-mail) of the visit date and the agenda. The agenda should include all issues to be addressed in the visit (e.g. pending queries and clinical processes that will go to be reviewed in the visit). This information should be submitted in advance to ensure that the clinical processes necessary for the review are available on the day we scheduled.
- Review the situation of SAEs occurred at the site and last visits performed by the patients, to determine expected Source Data Verification (SDV) to be performed for each patient;
- Review discrepancies that have arisen to site since last visit. These discrepancies should be reviewed before the monitoring visit in order to check what is asked by Data Manager (DM) on each request. In case of doubt DM should be contacted in order to confirm how the discrepancy should be clarified by the center. If the study is going through a database lock is very important inform DM in advance that CRA will make a visit to the given site on any given day in order to allow them to send all pending issues and discrepancies raised to this site and, consequently, to allow that everything is solved until the deadline (according with timelines).
- Review the new information to be provided to the investigator and study team about the study;
- Review the status of trial supplies and study IMP as well as respective documentation to be provided to the site during the visit;
- Review the list of issues to be discussed and reviewed at the investigational site as well as prepare essential documents to update ISF and PhF (e.g. Updated Investigator Brochures; correspondence between sponsor and site, CRA and site and with CEIC/INFARMED; acknowledgement of receipt of materials to the site and new documents sent by sponsor (newsletters, safety annual reports, etc.)

During the site visit, the activities developed were:

- Revision of ICFs;
- Revision and Update of ISF and PhF;
- Perform SDV accordingly Monitoring Plan agreed with sponsor and collect CRF pages, when applicable;
- Review electronic source documents;
- Review CRF (electronic or in paper) data and resolve any discrepancies, if existent;
- Check if there were any deviations and/or protocol, SOPs, GCPs and other applicable regulatory requirements violations;
- Check for all AEs occurred per patient;
- Verify that the receipt, use and return of trial supplies and investigational products were being controlled and documented by the study authorized personnel;
- When local laboratories are used, ensure that laboratory quality certifications and reference ranges are valid and updated for the parameters required per protocol;

- When central laboratories are used, ensure that all samples are being sent and procedures are correctly followed and documented;
- Verify that facilities and equipment remain in the required study conditions;
- Verify any changes in the study team and train any new team member to be delegated by PI;
- When necessary, other departments involved in the study should be visited (e.g. pharmacy and radiology) to ensure that the required study procedures are being followed accordingly in such locations. In the pharmacy case, it should be made accountability of medication, verification of storage condition (e.g. temperature and humidity) and expiry date, and verification of medication dispensing and return per patient. Beyond this, it should be ensured that the information about the compliance of each patient is sent to the investigator. In most cases, Investigational site and pharmacy are physically separated. However, information must be passed to the PI in order to know if patient is taking correctly the medication. CRA has to encourage this communication between the Investigator and pharmacy teams. In cases of blinded and unblinded CRAs, the unblinded CRA must inform the pharmacy about the importance of having communication about the study with the PI.
- Sign and date Monitoring Visit Log
- Verify essential study forms such as, authorization log (if there is any new study member on site team) and patient identification log (to be filled ongoing with the identification with all patients included);
- Confirmation the randomization codes integrity.

Sometimes due lack of time, it was not possible to accomplish all these activities during a monitoring visit. In these cases, the priority was ICFs and the safety information verification. I think that these are the most important and essential aspects of the monitoring visit. Then, SDV was performed and CRF reviewed. The rest can be made ongoing throughout the study.

During my experience in the sites, I have noticed that ICFs are the most critical process and where sites often make mistakes, such as, errors in dates, signatures in the wrong fields and PI signature/date made before patient signature/date. In these cases, it was necessary to refresh PI about the information process of obtaining ICFs.

Along my experience I have realized that although there are standard basic procedures to perform the monitoring visits, each study has different characteristics and in each one of them it is necessary to perform very specific procedures. In some of the studies that I have accompanied, I had paper CRFs and in the other I had electronic CRFs. In the studies where I have worked with paper CRFs, the original must be collected and sent to DM, a copy must be sent by fax to a sponsor/CRO platform and then keep it in the CRF. In the case of electronic CRFs, the procedure is totally automatic and there is no need to go to site to collect CRFs.

After the visit a report must be performed. My reports were all made in sponsor platforms which eliminates the necessity of sending the report manually to sponsor. Also, a follow-up letter is always sent to site.

Beyond monitoring visits, it is very important that CRA maintains a regular communication with sites in order to keep up to date on safety information, recruitment or other important information that may arise. This communication must be always documented. In some studies

there are Telephone Contacts Report sheets that must be filled for any contact made by telephone with the site teams.

2.2.4. CLOSE-OUT VISIT

During my curricular training I had the opportunity to prepare and execute a close-out visit.

A close-out visit is prepared when (25):

- The study is concluded, in accordance with Protocol;
- The sponsor decided to interrupt the study in all investigational sites (as a result of a interim analysis) or in a single site (e.g. as a result of recruitment failure);
- The Investigator, Ethics Committee, Administration Boards or Health Authorities may request the interruption of the study or the investigational site participation in the study.

The close-out visit that I have prepared was made following the study completion in accordance with protocol, with also the sponsor authorization and the confirmation that no more data queries would be raised from data manager. In certain cases and upon sponsor request, the close-out visit can be performed before database definitive lock. In these cases a declaration regarding the availability of the investigator to resolve queries after close-out visit should be obtained by the CRA.

The first step was to schedule the close-out visit with the site team, and after that to prepare the site visit. The preparation of this visit should follow the procedures used for any monitoring visit described above. Thus, in addition I have taken the following points into account:

- Confirm in advance the meeting time and place, as well as, send a meeting agenda and a confirmation letter which should detail the aims of the site close-out visit and request all necessary trial supplies and materials, including investigator file, to be available for the visit;
- Arrange a visit to the departments also involved in the clinical study (e.g. pharmacy). I have experienced that not always the CRA can arrange these visits in the same day. In my case, due to holiday periods of the investigator and the pharmaceutical and, consequently due to unavailability for the same day, I had to do the site close-out visit on two different days.
- The Trial Master File must be reviewed in-house to reconcile the documentation available and to identify any documentation that may have to be obtained from/or delivered to the investigational site;
- The payments to investigational team should be reviewed in order to understand and assure that they were all already performed.

As I mentioned above, the site close-out visit was performed in two different days. In the first day it was only possible to meet with investigator and study coordinator. Thus, as it was not possible to meet with pharmacist, it was decided with the sponsor that the first visit would be reported still as monitoring visit and then it would be schedule a formal close-out visit (when scheduled with pharmacist).

Yet, on the first day of close-out visit, the following items were verified and discussed:

- ISF – All documents included in ISF were verified and it was ensured that all have been correctly completed and archived. Some documents must be updated and collected for the Trial Master File (TMF) and left copies in the ISF (e.g. Authorization Personnel Log and Site Visit Log). In other hand, there are others that must be in the ISF and copies must be provided for the TMF (e.g. Patient Screening & Enrolment Log). It should be noted that Patient Identification log is the only document that remains exclusively in the ISF. For missing documents, a note to file was generated in order to document the reason of its absence;
- CRFs – All CRFs were verified in order to ensure that all filled CRF pages have been collected (in this case because it they were paper CRFs) and that investigator kept a full copy of each patient;
- Queries – It was verified that all queries were resolved to date;
- SAEs – It was verified that all SAEs have been reported properly identified, reported, notified and followed-up as much as possible by gathering the last information available in case there is any update information since last follow up;
- Biological Samples – It was verified if all biological samples were shipped to central laboratory and if the records of sample shipping were completed and properly archived;
- Patient Identification Log – It was verified if this form was completed and archived in the ISF;
- Storage of ISF, CRFs copies and source documents in a safe and restricted access place according with the period of retention defined;
- Financial Disclosure Form – It was reminded that investigator is responsible to notify the sponsor if changes to the Financial Disclosure Form occur until one year after completion of the study as defined per protocol;
- Audits and Clinical Study Report – It was discussed the possibility of an audit by the sponsor and/or inspection by Health Authorities after the site close-out visit and the necessity of include the Clinical Study Report in the ISF when it has been finished.

In close-out visits, CRA should also ensure that any equipment provided to the site for the purpose of study conduction was returned on this visit. In this case due the longevity of the study, there was no equipment provided and, consequently, nothing to return.

At the final of this visit all binders of ISF were clearly labelled with the following information:

- Eudract Number (if applicable);
- Protocol Number;
- Name of Sponsor;
- Name of Investigator;
- Investigational Site Identification;
- Archiving End Date, in accordance with applicable legislation/sponsor (fifteen years, in this case).

After this visit a site visit report was sent to sponsor (within 10 working days) and a follow-up letter was sent to investigator, where it was mentioned that the scheduling of the formal close-out visit remained pending until it will be scheduled with pharmacist in order to review the PhF and IMP records.

After the scheduling of close-out visit with pharmacist, the formal close-out visit was performed and the PhF and IMP records were verified. The activities performed regarding the PhF were similar to the ones held during ISF revision, such as, verify if PhF was up to date with all documents correctly completed and properly archived and keep it archived together with Investigator File. In this case under pharmacist request, PhF was verified in pharmacy and after sealed, was transferred to the Investigational Site Department where ISF was archived. Thus, all study binders were kept together under the responsibility of investigator. In other cases, PhF is kept under the pharmacist' responsibility and he/she is responsible for keeping the PhF in a safe and restricted access place until the end of the retention period. In these cases, CRA must ensure that PhF binder is clearly labelled with the same information described for the Investigator File binder. The location of the PhF, either archived under the responsibility of the investigator or the pharmacist should be clearly mentioned in the close-out visit report.

Regarding IMP, it was verified if the Investigational Product Dispensing Log was completed and if there any missing pages for the TMF need to be retrieved. A final accountability and reconciliation of the entire quantity of IMP received on site, used, not returned and not dispensed was performed.

After the formal close-out visit a site close-out visit report was performed and sent to sponsor also within 10 working days. A follow-up letter was sent to Investigator with the significant issues found during the visit and the required actions to be performed. The site close-out visit report was archived in the TMF.

Beyond this, a letter was sent to the Regulatory Authorities and the applicable Ethics Committee in order to notify the completion of the clinical study. This letter was accompanied with the Declaration of End of Trial, which must be sent by international team and submitted to CEIC within 90 days since the date considered as the end of trial date, in this case this date was the last patient last visit.

After all close-out visits performed, a notification must be sent to CEIC in order to inform that all sites are closed.

2.2.5. OTHER ACTIVITIES

In addition to the activities outlined above, in the CT monitoring there are other important activities carried out throughout the life cycle of the CT, namely, documents submission to competent authorities; archive and documentation management; and audits and inspections.

- **Documents submission to competent authorities**

As defined in Law nº 46/2004 of 19th August, a clinical trial can only be performed if there was a previous authorization from INFARMED and a favourable opinion from CEIC. It is also necessary an authorization from each of Administration Board of the sites and from CNPD.

During my curricular training I had no opportunity to execute all the process of submitting a request for opinion/ authorization. However, I could help and accompany other monitors that have prepared these submissions which are a very complex and slow process. These submissions are associated with a previous recovery and organization of all essential documents which are required by the authorities to submit the study and are related with the clinical trial, the IMP and in particular with the sites and personnel.

Beyond this, I had the opportunity to perform a request for opinion of a non-substantial amendment to the ethics committee. In practice the process is very similar to what is done at the time of submission of clinical trial. The difference lies in having a much smaller amount of documentation involved and, in this case, I only have notified CEIC.

Thus, all these submissions are oriented by the "Standards to be taken by applicants on the format and content of the request for an opinion from CEIC to conduct clinical trials with medicines for human use, notification/ request for amendment, notification of adverse events and declaration of end of trial". This document is in compliance and meets the requirements of the Law no. 46/2004 of 19th August and the Directive 2005/28/EC of 8th April. It also describes the information that may arise during the clinical trial, which must be submitted to CEIC for review or knowledge (26):

- New developments related to the trial conduction or IMP development, where they are likely to affect the participants' safety;
- Adverse reactions notifications;
- Situations where the trial is suspended or prematurely terminated by the sponsor. If INFARMED suspend or prohibit the clinical trial, CEIC should be informed.

Substantial amendments occur when there is relevant information that leads to change in the clinical trial conduction and may involve changes to the protocol or new information related to the scientific documentation that supports it. The amendments are substantial when associated with significant impact on the following (26):

- Security or physical/psychic integrity of participants;
- Scientific value of the trial;
- Conduction or management of the trial;
- Quality and/or safety of the IMP used in the trial.

Substantial amendments must be notified to CEIC, INFARMED and, in some cases the CNPD (e.g. if new data needs to be collected it is necessary to also perform a submission to CNPD). In other hand, it is not mandatory to notify CEIC or INFARMED regarding non-substantial amendments, but the process should be available in the trial master file to consultation in case of audit and inspection. However, I have verified that the companies define as default procedure always notify CEIC and INFARMED of non-substantial amendments. These notifications not always are performed individually because they can be submitted along with other notifications and amendments as agreed with the sponsor.

Sometimes sponsors' definitions of substantial and non-substantial amendments are in conflict with national requirements. It is always necessary confirm if the sponsor and national authorities definitions are the same. The process of submission should begin only after this. Anyway, sponsor can only implement the amendments when CEIC gives its favourable opinion and INFARMED does not present any objection.

As I mentioned above, I had the opportunity to perform a non-substantial amendment notification to CEIC. This amendment was regarding a new Investigator Brochure (IB) which in comparison with the previous one, presented a risk-benefit ratio that remained the same. As so, it was performed a submission package (paper and electronic) which consisted in a cover letter and

a copy to be stamped/signed and returned to company; and a CD-ROM with the new IB. It was also prepared an exact copy of the submission package to archive in TMF, including paper document and CD-ROM.

According with Law no. 46/2004, for all requests for opinion/ authorization the reasoned opinion must be reported to the Ethics Committee, the applicant and the INFARMED, within 60 days of receipt of the request by the Ethics Committee and INFARMED. However, if INFARMED/CEIC ask the applicant for information or documents complementary to the request, the period referred stops until receipt of the information or documents requested.

During my experience as CRA I have noticed that CEIC in most of the cases does not meet the deadline of 60 days and usually raises many issues that long delay the whole process in comparison with other countries. This can be a big concern in that it commits the conduction of clinical trials in Portugal.

Since most of clinical trials are multinational with competitive recruitment, if the approval of the trial in Portugal exceeds the previewed time, the recruitment period is somewhat diminished when compared with the other countries. The consequence is that sometimes it is impossible to include all foreseen patients in such a short period of time and, in a long term, international teams may decide not to involve Portugal in further studies.

There is an added difficulty after the release of the conditioned opinion/ approval from CEIC and INFARMED, which relates to the submission of financial contracts. This is because each institution has its own contract specific templates and different assessment and negotiation response times, making the process cumbersome further reducing the time of recruitment.

Portugal should turn more competitive in CTs setting and in recruitment since it could be passed over by other countries. We already assist to the situation where Portugal is not, in general, considered within the first layer of Countries to be selected for Clinical Trials in many therapeutic areas (27).

Another issue that I have verified and that can also delay the sites initiation and recruitment period is related with financial contracts. After favorable opinion/authorization of clinical trial by the Sites Administration Boards, the executed financial contracts of each site must be notified to CEIC and INFARMED. Following that CEIC will then release the formal favorable opinion for the initiation of each site. This final and formal approval is released on a site by site basis and dependent on each site Contract notification.

- **Archive and Documentation Management**

Along all clinical trials, numerous essential documents are generated in the study which allows assessing the trial conduction and the quality of generated information. These documents reflect compliance with GCP and with all regulatory requirements by the investigator, sponsor and CRA. Thus, it is essential to maintain this documentation updated on TMF, file that contains all the essential documents, before the study starts, during its driving and after its completion.

The archiving of these documents on TMF is made in accordance with sponsor or CRO SOPs, when applicable and as initially agreed. TMF is usually in the sponsor facilities and the CRA is responsible for keeping this documentation updated. When studies are international, the documentation must be sent on a regular basis with a transfer form of documentation for a

central archive. There are cases that sponsor only require the submission of TMF at the end of the study. In case of local studies, TMF is kept in sponsor or CRO (if delegated) facilities and it is only necessary to archive and keep the TMF updated.

Throughout my experience I have noticed that it is not always easy to keep the file well organized and updated, especially in long-term studies and where several handovers may have occurred. In these cases, when a revision is made it is usually found that there are documents that are missing and are often no longer available to be recovered. For these cases, the only solution was to write a note to file documenting the situation and the reason why documents are missing.

CRA has also the responsibility of sending all relevant and essential documentation to site. However, it is investigator's responsibility to maintain and update the ISF. There are some documents that only exist in ISF and which are essential for the assessment and traceability of the study. For example, as mentioned before the "Identification Patient Log" is archived only in ISF and it is very important in that it is the only form which makes the connection between the patient real identity and the participant coded identification in the study. Along my experience I have found that many investigators (especially when there are no Study Coordinators) do not give due importance to the file and sometimes it is the CRA that takes on the role of keeping the file updated.

- **Audits and Inspections**

During my curricular training it was not given me the opportunity to participate in a preparation of an audit/inspection to a site. However, I could help other CRA in the revision of TMF in order to prepare it to an internal audit. The main idea that I have retained after this task is that an audit preparation should be performed since the beginning of the study. As I said in the topic before, it is crucial that CRA archive and control all essential documents on a regular basis.

After the audit, I had access to audit report and all founded issues were discussed with my line manager. For me it was very important once it allowed brainstorming and review of some specific and important procedures that sometimes failed to be accomplished.

3. DISCUSSION

In this topic I will do a description of my experience in terms of what I have done, the tasks that I could not perform and the competences/skills acquired during these 10 months.

First I will resume the clinical areas and study phases where I was involved, and then I will describe the encountered difficulties and possible key-factors for success as CRA.

According to my point of view and my experience I will also make a brief description of the main differences found as CRA in a CRO versus Pharmaceutical Industry, and finally in this topic I will give my opinion regarding the future of the clinical trials/ monitoring processes in Portugal.

3.1. ABOUT MY EXPERIENCE

During my curricular training it became a fact that the knowledge acquired and capabilities developed (such as verbal and non-verbal communication skills; ability to develop activities in teamwork; and to find solutions on an autonomous way) in the Biomedical Sciences degree and in the Pharmaceutical Biomedicine master's course, were very useful and essential to achieve the goals I had set.

As CRA and also member of a company, the understanding of how the companies are organized, how each unit adds value to the business, the reading of SOPs and the trainings received were essential to feel like a team member who has a clear idea about what goals should be achieved, what are the difficulties and what are the profits. Thus, in each company that I have worked, I felt like a team member who is working for a common goal and under a common mission and values.

I have started my activities in Eurotrials in the Clinical Trials department (mono-disciplinary experience) and as mentioned before, I have also had the opportunity to understand how Biostatistics and Data Management departments work (cross-disciplinary experience). Despite of this very brief cross-experience and based on a theoretical component, it was important to understand how information flow is made from/to these two departments and how they connect with the others of the company.

During my experience in Eurotrials, there was the opportunity to go to work to the client under the outsourcing regimen. It was then that I started working at Roche. This allowed me to meet a different perspective on the CRA work in the pharmaceutical industry and recognize the differences.

Regarding my mono-disciplinary experience, as CRA I was involved in 12 clinical trials in several areas and in different phases. For me it was extremely rewarding and motivating to work in clinical areas as diverse. I have realized that although all therapeutic areas require much effort of a CRA, there are some that are generally more cumbersome to CRA/site team, in particular, the oncology which has almost always a lot more parameters and criteria to control and monitor in comparison with other pathologies. Therefore, I feel that I was fortunate to have worked mainly in oncology, since it prepared me to work in other easier areas.

Although I have not worked in a Phase 1 study during my training, I have had the opportunity to see other CRAs working and I have concluded that these kind of studies usually are conducted by more experienced CRAs once they focus mainly on safety and tolerance to the drug and are the

first contact of IMP with humans. A constant observation of the participants must be done during this phase in order to accompany all signs and symptoms derived from the low doses of IMP given in a small number of people. The participants of these trials are usually healthy, although for some drugs, the first experiments in humans are made in patients with the disease that the drug is intended to treat. The dose of the new drug is gradually increased during the first phase to allow the researcher to measure the participant's clinical response to the drug, if the drug is sufficiently absorbed, how long the drug remains in the bloodstream after the administration and what dose levels are tolerable and safety (18).

Beyond this, throughout my training I had the opportunity to develop the different activities inherent to the phases of a clinical trial life cycle (Feasibility, Initiation, Monitoring and Close-Out). As previously presented, I did not perform activities in the study qualification phase. However, I could understand that the qualification visit is not always performed due to low budget. In these cases, the initiation comes just after the feasibility. This can translate into problems of poor site selection since, at this time the feasibility process is done through surveys which go directly to sites and do not always reflect the reality of them. The CRA, someone who in fact knows how the site really is and how the teams usually work has more than ever a passive role in this process. Sometimes, in cases where there are no qualification' visits, some sites are selected and actually do not meet all the conditions to insure a satisfactory clinical trial conduction and commitment.

Along my training I have realized that although CRA can work in several clinical areas, with different study phases and with different teams, there are some aspects that does not change and which are transversal to all studies, in particular, the strong regulatory burden which began since the study conception, implementation, and development until the conclusion of the studies. The main objective of this regulatory burden is to ensure the protection and welfare of participants and maintaining the integrity of scientific results.

In addition, I have noticed that CRA's role and responsibilities extend beyond those defined by the ICH-GCP and regulatory requirements. The diversity of functions that the CRA performs forces to adopt a pragmatic method of working, organized and responsible where the supervision of clinical trial must be balanced with the relationship and trust established with the study and site team. CRA's time is divided between the office and sites and a good CRA must be someone who knows how to work in a team and must have good interpersonal skills, such as good communication, flexibility and assertiveness. Throughout my training I had the opportunity to work with sites with a very good organization (infra-structure and human resources) and the opposite. This allowed me to conclude that a structured, experienced, trained and motivated team is able to conduct the clinical trial more easily in compliance with protocol and all legal requirements. It also allows me to conclude that in sites where a clinical research culture is implemented, the study site members are more enhanced with the study and the objectives are achieved with low time-consumed and less CRA effort. I have also verified that when a long time as passed since the beginning and the study becomes old, the study team loses motivation and commitment decreases. In these cases, despite of all characteristics mentioned before, CRA has to be creative and try to motivate the site team.

In addition to this, the CRA must make a constant update on knowledge and training in order to be prepared for the different scientific areas and procedures which will have to deal with in professional life. Fortunately I was able to attend numerous training and courses which helped me to consolidate the knowledge acquired during the degree and masters' course.

It is important to clarify that the opportunity I was given in Eurotrials and Roche as CRA allowed me contact with two very structured environments and with a very-well organized procedures. Therefore, along my training I had no opportunity to contribute to major improvements because both host companies have a vast experience. Despite this, as I became autonomous, I was able to manage my work independently and anticipate and prevent problems, for example, choosing to make additional visits to the sites.

3.2. ENCOUNTERED DIFFICULTIES AND KEY-FACTORS FOR SUCCESS

Along my curricular training I could prove that the acquired theoretical background that I have acquired previously, although extremely useful in the development of all tasks, does not give a real idea of what will be the actual business practice and the real working environment.

During my experience in accompanying other CRAs in various tasks, I have realized that each one has a very different way of working and organizing, and quickly I realized that I would have to find a way of working that suited me best. Although it seems a detail, how the CRA organizes the work and information is extremely important since, as mentioned earlier, in this area there is always a lot of essential documents being generated, many parameters to control and lots of information to monitoring. A good organization of all information and well-established procedures are the basis for the CRAs' success.

During my experience I always started to work in clinical trials which had already been monitored by another CRA(s). This can be a very challenging situation because despite of having always a handover meeting, there are issues that are not passed to the new CRA due lack of time or forgetting. Thus, the new CRA sometimes is surprised by problems that already existed but were not documented. This problem is increased when the studies are long-term studies and have passed by many CRAs. For me, it was very important to carry out handover visits and in some cases one visit would not be enough to have an idea about the real site status. In these cases, a second visit should be made. In all cases, I think that is very important to document all issues and pending problems of the sites, being aware that the handover well accomplished is a key-factor for success of monitoring and, consequently, of clinical trial.

The real lack of time of some investigators for clinical trials in which they are involved usually results in delays and minor mistakes in conduction of the study, for example, filing documents incorrectly or with a large delay. It is very difficult to develop activities with a site team who has never time to the study and who is almost always unavailable to resolve study issues. In these cases, the CRA has to be patient but active in order to resolve the situation, either by motivating the investigator for the study or advising the inclusion of someone in the team that actually has time to study and to whom he can delegate tasks.

In general, there are several essential characteristics that site should present:

- There must be time and availability;
- Teamwork;
- Training;
- Experience;
- Patients;
- Logistics.

Beyond this, it is known that clinical trials depends essential of multivariate conditions, so CRA must be aware about key factors to achieve the best conducting a clinical trial and give more importance to them, as well as, critical study phases/aspects like feasibility, recruitment, investigational team and accompaniment by CRA/ sponsor to site team.

3.3. PHARMACEUTICAL INDUSTRY VS CRO: MAIN DIFFERENCES ABOUT BEING A CRA

Fortunately during the curricular training I had the opportunity to develop activities as monitor through two different perspectives: CRA in a CRO (Eurotrials) and CRA in a pharmaceutical industry (Roche). I will describe below the main encountered differences.

The reality provided by the training in a CRO as Eurotrials showed to be an asset in the acquisition of knowledge and practical skills for my professional development as competent and interested in monitoring clinical trials. In providing services to different sponsors, each one with its specific methods and procedures of work, Eurotrials gave me the opportunity to participate in different trials in different phases of development. This variety of phases, studies, clinical areas and methodologies promoted a growing knowledge and a rapid improvement on my technical, scientific and personal skills.

The experience at Roche was also the enhancement of personal and professional level. Although I have been undergoing trials in follow-up phase which the tasks flow was decreased, on the other hand, I won autonomy at Roche. I began to manage my tasks more autonomously and to carry out monitoring visits alone.

Regarding monitoring visits, it was the point where I noticed the most difference. The frequency of monitoring visits in CROs is determined for each study with the sponsor and defined in the study contract between sponsor and CRO, and in line with Clinical Monitoring Plan. However, the frequency for a specific investigational site could depend on the patient enrolment rate and site performance. Therefore, the CRA should discuss with Project Manager and/or sponsor, as appropriate, the adequacy of the monitoring visits frequency during the study contact progression. However, sometimes in international studies, the international study team is not within the reality of the Portuguese research sites, and compares Portugal to other developed countries with a more elevated level of conducting clinical trials. Thus, I found that they cannot always understand why CRA have to make an additional visit, when it is real necessary. I found that this is an advantage of working directly on the sponsor, since the people who approve the visits are directly working with CRA and knows very well the reality of the Portuguese sites and hence the need to allow for an additional visit.

Another difference found is that the CRA in the pharmaceutical industry often has access to the practical rationale that is behind the development of the study. For example, there are some patients who responded very well along many years to a medicine in a complex pathology and they will stop to take it just because the study where they were included will end. The pharmaceutical industry has the possibility to make an extension study that enables this group of patients who would have to stop taking medication have the possibility to continue to take it. In these cases the CRA can help identifying these patients in Portugal and help to identify the real benefit of these trials.

Other aspect that is very different for the CRA who is working in a pharmaceutical company is that, as opposed to a CRO, there is a marketing department which sometimes has indirect influence on

how the sites are strategically chosen to clinical trials. This means that the sites are chosen by clinical trials by the medical department, fully independent of the marketing department. Yet, this later department eventually add some pressure to choose or maintain certain sites accordingly their marketing strategies. Thus, sometimes unfair situations can arise in the sense that not all sites where a large quantity of drugs is sold are good in the conduction of CT; and in practical terms, this situation can only lead to an extra effort by the CRA in order to ensure a good CT conduction, even if the site does not cooperate as it should and as initially planned.

3.4. MONITORING: VISION ABOUT THE FUTURE

Clinical Trials in Portugal are facing some challenges. The regulatory demands have been increased, other countries offer better conditions to run clinical trials, there is a decrease of innovative drugs, and clinical trials demand more resources (28). According to these facts, there is a high probability of clinical trials diminishing in Portugal (29).

My experience has shown that in fact there are many gaps and challenges in clinical research in Portugal which must be overcome. It is verified that early clinical trials are not usually performed in Portugal, while phase III trials are the most performed. This is directly related with the fact that the majority of clinical trials performed in Portugal are funded by pharmaceutical industries and very few funded by academic institutions. This means that probably most R&D developed in these institutions is not translated into clinical research.

Beyond this, as opposed to other countries, the hospitals do not usually show clear policies, motivation, interest and autonomy in carrying out the clinical trials. In addition, they have a lengthy and complex bureaucratic process of approval which has not standardized procedures and are not equal for all hospitals. As I could verify, a submission process to an Administration Boards can take months to be dispatched.

Clinical trials bring many advantages for any country. Because of them, many patients have the opportunity to be treated with innovative drugs before their marketing authorization; the investigators have the opportunity in advance to improve their knowledge regarding new treatments, their benefits and risks; they also offer the opportunity to hospitals to use new technologies and know-how. For this and many other advantages, Portugal has to change.

It has been already observed a pressure of international headquarters of pharmaceutical companies in order to align the procedures between countries, so that clinical trials in all countries could be successful and well conducted. Thus, some procedures have already been changed and implemented. For example, I have found that there is already an effort by some pharmaceutical companies in order to make the sites to get used to being more autonomous.

Thus, the monitoring visits tend to be reduced, the SDV partially made and e-learning trainings will be the standard way to give and improve knowledge. Thus, the CRA will have more time to be in the office and carry out only his/her tasks, on a continuous and closer basis. This intends to make the study well underway since the beginning, where all the people involved actually perform the tasks according to their responsibilities. In my opinion, with this concept hospitals will need to have a better organized study team and for investigators that really do not have time to conduct the study, a study coordinator will be crucial. Also, the concept of close-out visits face-to-face tends to be no longer applicable. In fact, if the study is well conducted from the beginning, all documents are reconciled and all issues are resolved in a continuous basis along the study. So,

many objectives of the close-out visit can be solved with continuous CT monitoring and this visit loses impact on the study in relation to what it has now.

Although initially going to be difficult to implement these changes, I think that in a long term they will benefit all. However, it is important that sponsors take already action, for example giving training and clarifying hospital administration boards and investigators in order to incentive the clinical research in Portugal.

4. CONCLUSIONS

This ten-month experience in Eurotrials and Roche proved to be a very enriching experience and extremely important in my continuous improvement and enhancement of my skills.

I have realized that my degree and master's course have given me a multidisciplinary background which allows me to perform the activities with some additional training. Thus, I think that Biomedical Sciences degree and the Pharmaceutical Biomedicine master's course allows me to work in any one of the areas carried out in the clinical research. Despite not having gone through all departments, I think the original purpose has been fulfilled in the sense that I could see what is done in each unit and how it is done.

Regarding the mono-disciplinary training, all developed work in the office or at the sites allowed me to understand this profession in practical terms, as well as the skills that a CRA should have. During this training, it was given me the opportunity to follow 9 clinical trials as Clinical Research Associate (CRA) trainee and gradually it was given me the opportunity to perform tasks more autonomously and hence to follow 3 clinical trials as CRA.

For this, I think that my initial objectives have been achieved.

After all this experience, I felt prepared to ingress in the working world and I really appreciated what I have done. My future objectives are the continuing acquirement of knowledge and improvement of my skills in order to be able to evolve and carry out any work of my interest.

I would like to point out that this whole experience was so successful largely because of the people who I have been involved throughout my learning path. Again I thank to the entire Eurotrials team the tenderness, support and understanding at all times, from the beginning; also to the entire clinical operations team of Roche, where I grew up and acquired a new vision of being a CRA.

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