Universidade de Aveiro Secção Autónoma Ciências da Saúde
Ano 2014

André Filipe da Silva Lopes Cardoso

ESTÁGIO EM COORDENAÇÃO DE ENSAIOS CLÍNICOS

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física e do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa.

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palavras-chave

Centro de Investigação Clínica, Laboratório de Farmacologia Clínica e Terapêutica, Unidade de Farmacovigilância de Lisboa e Vale do Tejo, Unidade de Farmacologia Clínica, coordenação de ensaios clínicos, monitorização de ensaios clínicos, farmacovigilância, revisões sistemáticas, ensaios clínicos, estudos observacionais

Resumo

Este relatório apresenta a minha experiência adquirida durante o estágio no Centro de Investigação Clínica do Departamento de Neurologia do Hospital de Santa Maria, simultaneamente com algumas atividades no Laboratório de Farmacologia Clínica e Terapêutica e na Unidade de Farmacovigilância de Lisboa e Vale do Tejo. O estágio realizou-se entre Setembro de 2013 e Junho de 2014.

O estágio insere-se nas actividades curriculares do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Neste relatório irão ser abordadas as actividades de coordenação de ensaios clínicos e estudos observacionais, bem como a descrição do processo que levou ao desenvolvimento de uma revisão sistemática.

No decurso do estágio, tive a possibilidade de pôr em prática os conhecimentos adquiridos ao longo do Mestrado, e aprofundar o meu conhecimento sobre as actividades de coordenação de ensaios clínicos e observacionais. Também tive a possibilidade de observar, ao longo do estágio, todas as vantagens que existem em se realizarem ensaios clínicos num centro de investigação mas também as dificuldades que estes centros enfrentam na condução de estudos clínicos e observacionais.

No elemento de escrita científica, tive a possibilidade de ter instrução de como desenvolver uma revisão sistemática, podendo assim executar uma investigação.

Em conclusão, o estágio permitiu-me contactar com o quotidiano de um centro de ensaios clínicos e pôr em prática o conhecimento adquirido na Universidade, servindo ainda como nova fonte de aprendizagem, preparando-me para o meu futuro profissional.

keywords

Clinical Investigation Centre, Laboratory of Clinical Pharmacology and Therapeutics, Pharmacovigilance Unit of Lisbon and Tejo Valley, Clinical Pharmacology Unit, CT coordination, medical writing, pharmacovigilance, systematic reviews, CT, OS

Abstract

This report presents my experience during an internship at the Clinical Investigation Centre of the Department of Neurology at Hospital of Santa Maria, together with some activities at the Laboratory of Clinical Pharmacology and Therapeutics and at the Pharmacovigilance Unit of Lisbon and Tejo Valley . The internship took place between September 2013 and June 2014.

The internship is part of the curricular activities of the second year of the Masters in Pharmaceutical Biomedicine, University of Aveiro .

This report will address CT and OS coordinating activities, as well as the description of the process that led to the development of a systematic review.

During the internship, I had the opportunity to put into practice the knowledge acquired during the Masters, and deepen my knowledge of the coordination activities of clinical and OS. I also had the opportunity to observe, along the internship, all the advantages that exist in CT which are conducted in a research centre but also the difficulties that these centres face in conducting CT and OS .

Regarding scientific writing, I had the opportunity to be educated on how to develop a systematic review, and thus perform an investigation.

In conclusion, the internship allowed me to contact with the daily life of CT centre and put into practice the knowledge acquired at the university, still serving as a resource for learning , preparing me for my future career .

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List of Abbreviations

AB Administration Board

AD Alzheimer's Disease

ADR Adverse Drug Reaction

AE Adverse Event

APIFARMA Associação Portuguesa da Indústria Farmacêutica (Pharmaceutical Industry Portuguese Association)

CAML Centro Académico de Medicina de Lisboa (Lisbon Academic Medical Center)

CIC-CAML Centro de Investigação Clínica - Centro Académico Médico Lisboa (Clinical Investigations Center – Lisbon Academic Medical Center)

CEIC Comissão de Ética para a Investigação Clínica (Portuguese Ethics Committee for Clinical Research)

CHDI Cure Huntington's Disease Initiative

CHLN Centro Hospitalar Lisboa Norte (North Lisbon Hospital Centre)

CIC Clinical Investigation Center

CIOMS Council for International Organizations of Medical Sciences

CNPD Comissão Nacional de Protecção de Dados (Data Protection National Comitee)

CNPG Clinical Neuropharmacology Group

CPU Clinical Pharmacology Unit

CRA Clinical Research Associate

CRF Case Report Form

CRO Contract Research Organization

CT Clinical Trial

e-CRF Electronic Case Report Form

EC Ethics Committee

EMA European Medicines Agency

EU European Union

FAP Familial Amyloid Polyneuropathy

FCT Fundação para Ciência e Tecnologia (Foundation for Science and Technology)

FDA Food and Drugs Association

GCP Good Clinical Practice

HSM Hospital de Santa Maria (Saint Mary's Hospital)

ICF Informed Consent Form

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IMM Instituto de Medicina Molecular (Institute of Molecular Medicine)

IMP Investigational Medical Product

INFARMED Autoridade Nacional do Medicamento e Produtos de Saúde (National Authority of Medicines and Health Products)

ISF Investigator Site File

ISO International Organization for Standardization

IV Intravenous

IVRS Interactive Voice Response System

IWRS Interactive Web-Response System

JNICT Junta Nacional de Investigação Científica e Tecnológica (National Board of Scientific and Technological Research)

LCPT Laboratory of Clinical Pharmacology and Therapeutics

MPB Master's Degree Pharmaceutical Biomedicine

MS Multiple Sclerosis

NCRU Neurological Clinical Research Unit

NME New Molecular Entity

OS Observational Study

PD Parkinson's Disease

PI Principal Investigator

REGISTRY European Huntington's Disease Network

SAE Serious Adverse Event

SC Study Coordinator

UA University of Aveiro

UFLVT Unidade de Farmacovigilancia de Lisboa e Vale do Tejo (Pharmacovigilance Unit of Lisbon and Tagus Valley)

VS Vital Signs

1. Introduction

Inserted in the second year of my Master's degree in Pharmaceutical Biomedicine (MPB), I applied and went through an internship at the Clinical Investigation Center (CIC) of the Neurology Department at *Centro Hospitalar Lisboa Norte, E.P.E. - Hospital de Santa Maria* (CHLN, E.P.E. – HSM) that had a duration of 10 months. Together with the training at CIC, I had the possibility to spend some time in the Laboratory of Clinical Pharmacology and Therapeutics (LCPT), workplace of most of the Clinical Pharmacology Unit (CPU) team and in the Unidade de Farmacovigilancia de Lisboa e Vale do Tejo (Pharmacovigilance Unit of Lisbon and Tagus Valley) (UFLVT). This internship came in the sequence of one year receiving theoretical training in a wide set of matters related with the drug life cycle such has Clinical Trials (CT), pharmacovigilance and regulatory affairs. Later in this report I will give a more detailed description of my training during this first year of my Master's Degree. I had a special interest in the area of CTs, so when I had the chance to have an internship in a CIC I immediately applied for it, setting as primary objective to learn and practice as a Study Coordinator (SC). During these 10 months of internship I was supervised by Professor Joaquim Ferreira and Professor José Carlos Lopes. Along with the description of the institution where I underwent my internship, in this document I present my activities, learnings and projects over these 10 months.

In order to better describe my internship I divided my report in different chapters.

Along with this brief introduction, **Chapter 1** is divided in two subchapters. In subchapter 1.1 I discuss the history, structure and mission of my internship's 3 hosting institutions. These were the CIC, CPU and UFLVT. My background training in the 1st year of my MPB and my internship objectives are described in the subchapter 1.2.

In **Chapter 2** I describe some aspects about CTs namely in what they consist, which are the different CT phases, how looks the current CT panorama in Portugal and, finally, which and what are the responsibilities of the main regulatory authorities in CT environment.

In **Chapter 3** I describe the training that I received as well the activities that I performed during my 10 months of internship giving a special focus to my training as SC.

In **Chapter 4** I make a description of the projects that I developed in collaboration with my colleagues from the CIC during my internship. These projects resulted in the writing of review articles which are aimed for being submitted for publication.

In **Chapters 5 and 6** are presented the discussion of my internship as well as the conclusions that I retrieve from my training, respectively.

The documentation and other resources that I consulted in order to help me to construct this report are referred in References.

1.1. Vision about the host institutions

As referred before, my internship was carried in three groups: CIC, CPU and UFLVT. In each one of them, different activities are performed but the professionals that work in these 3 institution all cooperate with each other mainly due to the physical proximity of these departments and because of the fact that some of these persons work in more than one of these working places. These three institutions have their own history but at some points they were and are related for the reasons mentioned before. At an institutional level, the CPU actually contains the CIC and the UFLVT. The organisation of these institutions is very recent so there are no literature references to that. Information about its history is not very well documented too. The information that I have about my hosting institution was in large scale available to me through verbal contact with person responsible for these groups and well informed of its history and current structure.

I will try to describe the history and the current panorama and activities of these three organisations in order to better explain the environment where I trained during this year.

1.1.1. Unit of Clinical Pharmacology

The LCPT is a physical space inside the Faculty of Medicine of the University of Lisbon (FMUL) that aggregates some groups of the CPU. CPU is an institution from the Instituto de Medicina Molecular (IMM) that comprises the Cochrane group which belongs to an international collaboration network composed by institutions and individuals intending to set new systematic reviews preparation standards, the CIC and the UFLVT. From these the only group that is not located in the same physical local, the LCPT, is the CIC as it will later be described.

Despite belonging to these different groups, the professionals that work at the CPU collaborate with each other in order to maximize the efficiency of the work developed. In general the groups collaborate in the CPU in order to produce investigator driven

research alongside with statistics, medical writing, project management and other support activities. The current leader of CPU is Professor Joaquim Ferreira.

This institution, however, did not always have this structure. Long before the appearance of IMM, a neuropharmacology section was created by physicians of the movement disorders group, namely Professor Alexandre Castro Caldas, Professor Virgílio Durão and Professor Cristina Sampaio.

Until 1967 it was difficult to get funding to research activities. The creation of Junta Nacional de Investigação Científica e Tecnológica (JNICT - National Board of Scientific and Technological Research) enabled financial support to research promoted by institutions of higher education and postgraduates fellowships. In 1995 JNICT was extinguished and was substituted only on a funding perspective by Fundação para a Ciência e Tecnologia (FCT - Foundation for Science and Technology) during 1997(1). FCT started promoting investigation from entities, research groups or individual researchers that proved to have a strategy for scientific and technological development inside Portugal(2).

IMM appeared in December of 2001 as a result of a fusion of efforts and activities from the Portuguese Institute of Oncology Francisco Gentil and five former research units from the FMUL.(3) Within these five research units could be found the “Lisbon Neurosciences Centre”, group from where it was launched the bases to the team where I developed my internship. It is located at the campus of the FMUL and is an Associate Laboratory of the Portuguese National Ministry of Science, Technology and Higher Education without any profit intentions. Its mission is to promote basic, translational and clinical research in biomedicine. The ultimate goal is to contribute to a better understanding of disease mechanisms allowing the development of new predictive tests, improve diagnostic tools and more developed therapeutic approaches(3).

It is possible to understand that through the years the financial support to the activity of the pharmacology group raised gradually. As mentioned before the current leader of CPU is Professor Joaquim Ferreira, which substituted Professor Cristina Sampaio, who was the previous director of this team, when she left the unit to become Chief Medical Officer of the Cure Huntington’s Disease Initiative (CHDI) Foundation. During the time when Professor Cristina Sampaio was in charge of the this group, it was not yet known as CPU but as Clinical Neuropharmacology Group (CNPG), a part of the Neurological Clinical Research Unit (NCRU) from the group of Neurosciences, headed by Professor José Ferro(4). Nowadays, under Professor Joaquim Ferreira work and with the

constant broadening of the activities of the unit in addition to neurological research, this unit became independent from that department, being only under IMM.

1.1.2. Clinical Investigation Centre

One of the subunits of the CPU is the CIC. Here I performed most of my work and training during my internship. This unit is the only part of the CPU that is physically present in the LCPT, being located on the 6th floor of the Neurology Department of CHLN, E.P.E. – HSM.

Here is where CT and Observational Studies (OS) of new drugs for neurological disorders and, sporadically, other interventional areas are conducted. Since a long time, once Professor António Damásio and Professor Castro Caldas started integrating clinical investigation, the hospital had CT in neurology but until 1999 there wasn't a specialized centre to receive these trials, which was implemented at that year by Professor Joaquim Ferreira.

In the beginning of this unit, its main focus was movement disorders related CTs but with time it started to receive more varied trials as it will be explained below. Until 2013, this unit was known has the movement disorders group of the CNPG, under NCRU but at that time, with the restructuring of CNPG and the change of its name to CPU, also the unit where CTs were being performed adopted the name of CIC.

The CIC team is composed by full time 2 SCs and a lab technician that work together with other health professionals such as physicians, nurses and the pharmacy team depending on the CT staff requirements. Their responsibilities are well defined according to ICH-GCP(5) and are presented below:

- **Investigators** are experienced clinicians which are qualified and trained to conduct CTs. Since there are CTs in several different diseases like Familial Amyloid Polyneuropathy (FAP), Alzheimer's Disease (AD), Parkinson's Disease (PD) or Multiple Sclerosis (MS), for each of these diseases different clinicians that work with the team assume the role of principal investigator (PI). During the CTs, the principal or sub-investigators are responsible for the recruitment of the participants, monitoring the patients during the CT by prescribing and controlling study medication, ensuring its safety, keep in tract of any possible Adverse Events (AE) and if necessary taking the decision of withdrawing the subject from the study;

- The **SC** is responsible for the entire logistic organization of the CTs inside the CIC. Visits preparation, patient follow-up and its instruction about study procedures are all under the responsibility of the SC. Additionally, it performs Electrocardiograms (ECG) to patients, checks Vital Signs (VS), processes biological samples, entries the gathered visit information in the Case Report Form (CRF), answers queries, contacts with Clinical Research Associate (CRA) handle financial aspects and oversee personnel, Summarizing the SC is like the glue-guy in the research team;
- The **laboratory technician** has the responsibility of collecting biological samples and processing them when applicable according with each study protocol;
- The **study nurses** normally work has backups to the lab technician in the task of collecting biological samples and also performs some specific activities such has catheterizing patients in trials where there is Intravenous (IV) medication or other needed support with the patients;
- The **hospital pharmaceuticals** are responsible for receiving, storing, dispensing and accounting the investigational medical product (IMP). In our specific cases, the prescription completed with the information obtained from the Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) can be sent to the pharmacy by email and a pharmacy assistant brings the IMP to the site. Then the investigator checks the batch number and when it matches with the number obtained in the IVRS, the IMP is delivered to the patient. Patients normally do not have to dislocate themselves to the pharmacy to receive medication once has been established a cooperation between the pharmacy and the rest of the research team. SC prior to each visit alert the pharmacy of which medication will be necessary and a carrier brings the medication to the site in order to deliver in to the subject. The main reason for this special care is due to the fact that the research involves patients with movement disabilities.

Since 1999, this unit as received according to records obtained in the centre 136 investigations, from which 104 are CTs and 32 are OSs. PD, Epilepsy, MS and AD represent around 80% of the total investigations performed in CIC since its formation but also trials in the area of FAP, Huntington's disease (HD), Dystonia, Spasticity between others can be found as illustrated in the graphic below. Note that in this

graphic OS are all reunited independently of its focus disease, being only the CTs divided in categories.

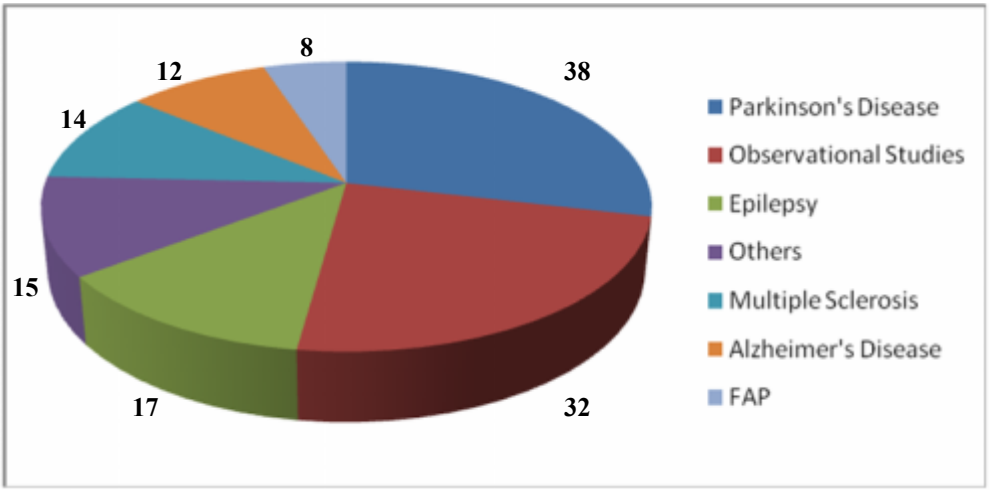

Figure 1. Distribution of CIC's CTs Number by Disease

Source: Records kept in CIC

In the beginning of this decade FMUL, the CHLN, E.P.E – HSM and the IMM joined to inaugurate a new institutional cooperation by creating the Lisbon Academic Medical Centre (CAML). This consortium intends that through the fostering of translational research, optimization of the use of resources either human or financial and by improving the collaboration between research institutions at a national and international level to give the best healthcare related products to consumers guarantying more years of life and with better quality(6). From this collaboration resulted a new investigational centre that is located at the 7th floor of the Neurology Department from the CHLN, E.P.E – HSM which will be prepared logistically and will count with an experienced staff in the area of CTs, composed in a part by the members of the CIC.

The name of the new units will be Centro de Investigação Clínica – Centro Académico Médico de Lisboa (Clinical Investigations Center – Lisbon Academic Medical Center) (CIC-CAML) and its objective is to receive CTs from all the medical specialties and congregate in the same place all the clinical research activity of the CHLN, E.P.E – HSM. This centralization will allow some benefits from which can be highlighted the fact that the contact and the sending of documentation or medication between Pharmacy and the CIC-CAML team well be easier than before, when the Pharmacy had to contact with the all the different services that performed CTs. Additionally, the diverse staff members that worked previously in different medical specialties related CTs are now joining in the same group and can share their knowledge and strategies to improve the efficiency of CT development. A high quality study centre will also be very useful to

attract more CTs from industry increasing the investment an enabling possible future investigator driven research.

1.1.3. Pharmacovigilance Unit of Lisbon and Tagus Valley

During my internship I spent 2 weeks in the unit of pharmacovigilance receiving general training about its structure, the importance of its activity, what procedures there are performed and which are the intended goals to reach annually by UFLVT. The activity of pharmacovigilance units is very important in order to assure the safety on the use of medication by the general population, since even knowing that the trials performed during the drug development ensure the efficacy, safety and quality of the product, they are performed in a small group of population when compared with the "real life" users of the medicine and Adverse Drug Reactions (ADR) may occur at any time.

This unit is located in LCPT and is supported by Autoridade Nacional do Medicamento e Produtos de Saúde (National Authority of Medicines and Health Products) (INFARMED) being one of the 4 Pharmacovigilance Areas of the Portuguese territories. In its area of influence, according to the 2011 Portuguese censos, there are 3659868 persons under UFLVT responsibility(7). It is responsible for processing ADRs reports sent by health professionals and general public from the Lisbon and Tagus Valley health region. With this and other procedures such as the promoting and divulgating safety control methods like spontaneous notifications becomes possible to monitor the safety of commercialized medicines(8, 9).

Additionally to this ADRs reception, UFLVT develops activities of training in order to aware the healthcare professionals and general public of the importance of reporting ADRs and explain how an ADRs is processed and which consequences and actions may outcome from these notifications. A periodic report about new ADRs is a part of the UFLVT activities such has developing some epidemiological studies about the Portuguese pharmacovigilance system(8, 9).

In the UFLVT work 4 professionals, one physician that is at the same time the head of the UFULVT and the clinical coordinator, two pharmaceutics and one administrative assistant. Each of them has their own responsibilities inside the UFLVT, contributing to an efficient work of this unit.

1.2. Masters Background and Training Objectives

The years that I spent in University of Aveiro (UA) both during my Bachelor in Biomedical Sciences and my first year of Master's Degree in Pharmaceutical

Biomedicine (MPB) were fundamental in order to have a high base of knowledge especially in what refers to CTs. This would reveal to be fundamental for quickly fitting into the clinical research team.

In my Bachelors, named Biomedical Sciences, I received a very widespread training but I have to highlight what I have learnt in the fields of physiology, chemistry and psychology because working on CTs required some skills that I got studying these matters. Regarding my MPB, I had several different modules such has Non Clinical and Clinical Development, Pharmacovigilance, Quality Systems, Regulatory Affairs, Project Management, Statistics and Ethics(10). In all of these matters I received very important information from highly qualified professionals which gave me an extensive set of knowledge in order to be able to work in very different areas.

After this year I had to apply for an internship and my main area of interest was CTs. I looked for opportunities of internship in this area having the doubt of either I wanted to train as a SC or as a CRA.

I ended up choosing to apply for an internship as a SC trainee at CIC and I performed an interview with Professor Joaquim Ferreira. I had the confirmation that I would be accepted for my training still during April. Since I would start my internship only in September I decided to gather all the information that I could about the centre. I researched and spoke with my older colleagues from my Master's Degree that previously had trained at CIC. I got to know that in CIC they perform CTs in the area of Neurology, that there works a multidisciplinary team and that when I would get there I would be in close contact with both the patients and with study promoters, which means Pharmaceutical Industry.

This led me to define some objectives regarding my internship even before I arrived to the center as follows:

- Receive training in study coordination - I wanted to know which activities I would have to develop in the future as a SC, what problems I would have to be ready to face in this activity and what strategies can be adopted to face this difficulties;
- Contact with the clinical research centre environment - With this I expected to observe how the centre is managed in terms of delegation of functions to the different healthcare professionals and what activities are performed in it;
- Apply all the theory lessons that I learned during my academic training over CTs, inserted in my Master's Degree, to the practice of study coordination.

When I first got to the CIC I was informed that I would have the opportunity to work with a multidisciplinary team. But at this point I could actually be presented to those persons who promptly made themselves available to help me in whatever I needed and teach me in their areas to help complementing my training. These professionals included SCs, physicians, psychologists, nurses, laboratory technicians, pharmaceuticals, statisticians and physiotherapists.

I was also informed that I would be able to work at the LCPT where several investigations are performed as I mentioned before through systematic reviews and meta-analysis and at UFLVT, where are processed almost all AEs notifications of the zone of Lisbon.

Finally, when I first contacted with a CRA I verified how complex and important their activity is to keep the quality and compliance with protocols of CT.

With this conjuncture I defined some other objectives adding to the ones that I set before coming to the clinical center. These additional objectives are:

- From contact with the previously refered healthcare professionals, obtain theoretical and practical training ih their areas in order to make me a more complete professional;
- Perform activities of researching and scientific writing at LCPT and receive some on-the-job training about pharmacovigilance systems at UFLVT;
- Understand and lear how to develop monitoring procedures from contact with CRA.

2. State-Of-The-Art

My background training enabled me with a set of knowledge in the area of clinical investigation that would reveal very helpful during my internship. There are some concepts that anybody working in this area should be provided with.

2.1. Drug life-cycle

The clinical investigation, which was my main area of training during this year is inserted in the medicines life cycle. I will briefly describe the different parts that compose this cycle, giving a special attention to the clinical investigation phase.

In order to develop a new drug several stages and procedures have to be followed in order to assess safety, efficacy and quality of the new molecular entity (NME).

2.1.1. Discovery

The first step is to discover a NME that possibly will originate in the future a new drug. Thousands or even millions of molecules undergo a screening procedure with the objective of founding to a certain biological target the correspondent lead.

A biological target is any structure or molecule, such as a nucleic acid or a protein, within a living organism which is intended to be matched by some other entity. A lead compound is a chemical compound that has a pharmacological or biological activity likely to be therapeutically useful.

This action of inducing an interaction between a lead compound and a biological target is intended to produce a therapeutic effect. After the identification of a potential lead compound, this goes through a process of optimization and validation in order to increase the probability of safety and efficacy of a future drug that can come from this entity. A process of patent application is then followed in order to guarantee that a potential new drug rose from this molecule or biological entity will not be developed by any other research team(11).

2.1.2. Pre-clinical studies

After the patent is conceded, the IMP advances to the stage of pre-clinical development where preclinical pharmacology and preclinical safety are assessed. This studies are developed both in vitro an in vivo models. At this phase the in vivo models are mammals such as rodents, dogs or monkeys. The species are selected depending

on the intended end of the research and which of the species, at the light of the current knowledge is believed that can more precisely simulate the drug action inside the human organism. The principal objective of the preclinical development of a compound is to assess its safety profile(12).

2.1.3. Clinical development

The next stage is the clinical development where are inserted the CTs. I will focus on this part because is my main area of interest and is my area of internship.

The concept of CT is relatively recent. In spite of that, several investigations were performed and could be considered as a proto CT(13). The first registry of something similar to a CT occurred when a British physician named Dr. James Lind designed and controlled in 1747 the first clinical investigation. For this he is called the father of CTs. He performed an investigation with 12 sailors when he was serving as a surgeon in a British naval ship. The objective was to assess why there was such a high mortality due to scurvy. He divided the 12 subjects with the same symptoms in 6 groups of 2and giving them 6 different scurvy treatments in addition to their normal diet: either cider, a weak acid, vinegar, sea-water, nutmeg and barley water, or oranges and lemons. Oranges and lemons proved to give the best results(13, 14).

Nowadays, CTs are much more complex and have a regulated definition. In the page 9 of ICH-GCP can be found that a CT is “any investigation in human subjects intended to discover or verify the clinical, pharmacology 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”. CTs can be classified either according to a sequential classification of the phases (from phase I to IV) or according with the objective: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use. The two classifications can be related to each other having some king of transposition but since one trial may occur in different temporal phases it is more correct to classify them according to the objective(15).

CTs can this way be divided as follows:

- Human pharmacology trials are usually identified with Phase I studies. These first-in-human trials of a new potential drug are carried out in healthy volunteers or in restricted groups of patients. The objectives are assessing the

tolerance, describing the pharmacokinetics and pharmacodynamics profiles of the drug, exploring the drug metabolism and interactions, and estimating the activity of the drug. Some examples of these studies are dose-tolerance studies, single and multiple dose Pharmacokinetics and/or Pharmacodynamics studies and drug interaction studies.

- The therapeutic exploratory studies are linked to Phase II studies and are normally conducted in reduced groups of patients. Its primary objective is to explore the therapeutic efficacy in subjects with the intended disease to treat. These studies are aimed to explore the use of the drug for the targeted indication, to estimate the dosage for the subsequent studies and to provide the basis for confirmatory study design, endpoints and methodologies. Some study examples are earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures and dose-response exploration studies.
- Therapeutic confirmatory studies, which are normally related with Phase III trials, have as primary endpoints to demonstrate or confirm the efficacy of the drug, to establish a safety profile, to provide an adequate basis for assessing the benefit/risk relationship to support licensing and to explore the dose-response relationship. Some examples of these studies are adequate, and well controlled studies to establish efficacy, randomized parallel dose-response studies, clinical safety studies, studies of mortality/morbidity outcomes, large simple trials and comparative studies.
- Therapeutic use studies or Phase IV studies begins after the drug approval. These studies have as objectives are to refine the understanding of the benefit/risk relationship in general or special populations and/or environments, to identify the less common adverse reactions and to refine the dosing recommendation. Examples of studies are comparative effectiveness studies, studies of mortality/morbidity outcomes, studies of additional endpoints, large simple trials and pharmacoeconomic studies(15).

Apart from CTs, there are other studies involving humans known as OSs. In these studies there isn't any pharmacological intervention, being based only in assessing health outcomes in groups of patients in accordance with an established protocol or research plan. Interventions received by participants in OSs must be related with their normal clinical practice and not with any particular therapy strategy involved with the research objective. Participants should not, as well, be submitted to any additional

evaluations. Data collected, thus shall be analyzed by epidemiological methods(16, 17).

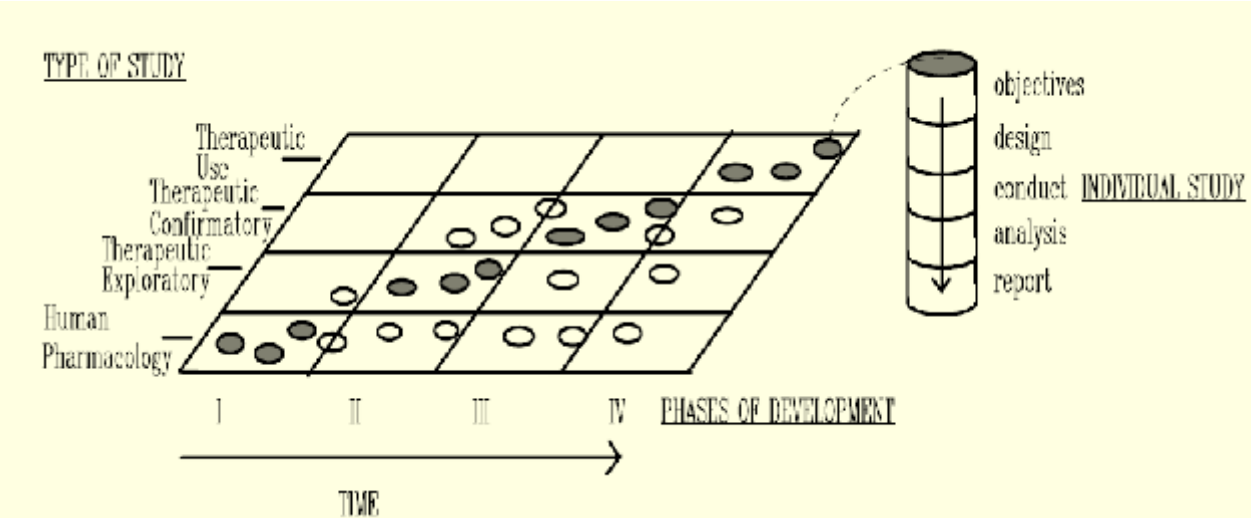

Figure 2. Clinical Development Phases

Source: Figure 1 of Reference 15

2.1.4. After commercialization

After proving its efficacy and safety, new potential entities can be proposed for a marketing authorization, and if approved can enter the market. After being commercialized, together with the normal therapeutic use trials that were mentioned before, there is a constant vigilance in order to detect, assess, understand and prevent adverse effects or any other drug-related problem. This process is known as Pharmacovigilance(9, 18).

2.2. Regulatory Authorities

The area of drug development and particularly the CTs are widely regulated. In order to better understand this regulatory environment, a brief description of some institutions is given:

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a combined initiative between regulatory authorities and the pharmaceutical industry from United States, Europe and Japan. Its goal is to discuss scientific and technical aspects of drug registration. By harmonizing the regulatory processes and obligations it ensures that safety, effectiveness, and high quality standards are applied in

new medicines development and that its registering is carried in the most resource-efficient manner(19);

- European Medicines Agency (EMA) is the regulatory agency of the European Union (EU) essentially responsible for protecting and promoting public and animal health. This process is executed by evaluating and supervising medicines for human and veterinary use. An important duty of EMA is to evaluate scientifically the applications for EU marketing authorizations. In what concerns safety and benefit-risk balance of medicines to be or already approved by a non-centralized procedure it assumes an arbitrary position. It also monitors the safety of medicines by the establishment of a wide Pharmacovigilance network and stimulates the continuous research improvement in pharmaceutical area(20);
- Food and Drug Administration (FDA) is the United States of America's agency responsible for protecting and promoting public health. The processes that lead to that end are reached by regulating and supervising food safety, tobacco products, dietary supplements and pharmaceutical products(21);
- INFARMED is a public institute included in the indirect administration of the State. This signifies that INFARMED is endowed with administrative and financial autonomy and has its own patrimony. INFARMED IP is a central body with jurisdiction over the entire Portuguese territory and acts by regulating and supervising the areas of drugs, medical devices, cosmetics and personal hygiene products according with the highest standards. Is mission is to protect public health and ensure access to health professionals and citizens to medicines, medical devices, cosmetics and personal hygiene products with quality, effectiveness and safety;
- *Comissão de Ética para a Investigação Clínica* (Portuguese Ethics Committee for Clinical Research) (CEIC) is an independent organism with the participation of different professionals connected or not with the healthcare activity which aims to guarantee the protection of the rights, safety and well-being of the CT subjects, by emitting an ethical opinion over the submitted research protocols. Also monitors Health Ethics Committees, receiving all applications for ethical review(22);
- *Comissão Nacional de Proteção de Dados* (Data Protection National Comitee) (CNPD) is an independent administrative entity with authority powers. Its function is to control and supervise the data processing always in compliance in

a rigorous respect for human rights and freedoms according to Portuguese law and constitution(23);

- The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental and non-profit organization recognized mutually by WHO and UNESCO in 1949. It has the purpose of helping in the reach of scientific goals of the international biomedical community in general and its specialized agencies. This is done by facilitating and promoting international biomedical sciences activities and working on the relations of the science community with the United Nations(24);
- International Organization for Standardization (ISO) is an independent and non-governmental organization constituted by representatives of the national standards bodies of 164 countries. Its aim is to help on simplifying the coordination and unification of international industrial standards(25);
- *Associação Portuguesa da Indústria Farmacêutica* (Pharmaceutical Industry Portuguese Association) (APIFARMA) founded in 1975, represents more than 120 portuguese companies responsible for Production and Import of Medicinal Products for Human and Veterinary Use, Vaccines and Diagnostics In Vitro with a view to solving common problems, the socio-development economic sector of the country and the improvement of health in Portugal and greater patient access to new therapies(26).

2.3. CT Regulatory Framework

Behind the practise of CTs there is a very widespread set of regulatory documents that serve as guidelines to the conduction of these research procedures either concerning medical aspects and ethical considerations. From these set of documents some can be highlighted due to its importance and transversally across all the CTs. The following list of guidelines and declaration is the base for the work of all the healthcare professionals within CTs.

2.3.1. Worldwide Documents

- In 1947 the Nuremberg Code was elaborated in answer to the atrocities committed during World War II, specially the medical experiments conducted in concentration camps by the Nazis where prisoners were tested without any kind of agreement. These experiments led to deaths and disabilities in thousands of

human beings. The principal aspect of the Nuremberg Code is the demanding that all CTs performed in a person must have his informed consent form (ICF)(27);

- The Helsinki Declaration appeared in 1964 in answer to the Thalidomide disaster in which thousands of babies born with abnormalities due to lack of knowledge about secondary effects in pregnant women when taking that drug. This declaration specifies a series of ethical principles for medical research involving human subjects in CTs. It suffered 10 amendments seven times since, with the last one having occurred in 2013, adopted at WMA General Assembly(28);
- The ICH-GCP E6 is a document which final version was issued in 1996 and intends to standardize clinical research in all three ICH regions: the United States of America, Europe, and Japan. Responsibilities of each participant of a CT, specifically the sponsor, the investigator and the CT coordinator amongst many others are described in this document(5).

2.3.2. European Legislation and Portuguese transpositions

- Directive 2001/20/CE, April 4th, also called the CT directive, specifies the requirements for the conduct of CTs in the EU. This directive was transposed into the Portuguese national law by the Decree-Law 46/2004 of August 19th(29);
- Directive 2005/28/CE, April 8th, lays the principles for Good Clinical Practices of experimental drugs for human use. This directive was transposed into national law by the Decree-Law 102/2007 of April 2nd(30);

- Directive 95/46/CE, October 24th, concerning the protection of patient data. This directive was transposed to national law by ordinance nº 67/98 “Personal data protection” and by Resolution nº333/2007 and this one regards personal data protection in CTs with medicines for human use(31).

Following the idea that all healthcare professionals working on CT must be familiarized with these documents, during my training in University I recurrently had references to these guidelines and I ended up applying them coming into this internship.

2.4. Clinical Investigation in the world

With a constant need of developing new medicines and acquire knowledge about the existing ones, CTs and OSs are increasing in number in a large scale. One of the sources that state this situation is ClinicalTrial.Gov that by the date of 3rd June 3, 2014 "lists 168,182 studies with locations in all 50 states and in 187 countries." This numbers show the incidence of research in the medicines area. This database also provides some data about specificities on these total numbers. It is stated that almost 80% of investigation worldwide are CTs and the remaining 20% are OSs. Considering the type of intervention, 53% are drug or biologic interventions, 21% have a behavioural directed study, 9% are related with surgical procedures and 8% are related with medical devices. Attention to the fact that each CT may have more than one type of intervention and that's why if we add the sum of all the categories the result won't be the percentage of CTs(32).

The numbers of registered and recruiting studies sorted by region are presented in the table below.

Table 1. Number of Worldwide Registered and recruiting Studies (32)

Location	Number of Registered Studies and Percentage of Total	Number of Recruiting Studies and Percentage of Total
Non-U.S. Only	75,868 (45%)	16,716 (51%)
U.S. Only	67,403 (40%)	14,211 (43%)
Not Specified	14,662 (9%)	----------
Both U.S. & Non-U.S.	10,249 (6%)	1,963 (6%)
Total	168,182 (100%)	32,890 (100%)

Over the years, the number of CTs increased. The figure below gives an idea on the much bigger dimension of the investigation nowadays when is compared, for example, with the beginning of the millennium. From 2000 to the present date we went from having 5635 investigations worldwide to 159207(32).

Figura 3. Number of Registered Studies (2000-present)

Source: ClinicalTrials.gov. Trends, Charts, and Maps 2014 (32)

Having this general numbers presented, it's now important to compare these results with the ones from Portugal and so the next subchapter is dedicated to give a view of clinical investigation in our country.

2.5. Portuguese CT Panorama (33)

When we compare the incidence of CTs in the Portuguese territory with the ones from Europe or even in the rest of the world, we notice that there are differences in the number of centers, participants and money invested or profited. This may be explained by how small our country is compared with other countries that perform much more. Other reasons can be pointed for these discrepancies. It is important to analyze the data and find the pros and counters of how clinical investigation is performed and supported in Portugal.

Most of CTs performed in Portugal are promoted by R&D multinational enterprises. During the year of 2012, indicators show that these enterprises invested in CTs in Portugal a total of 36 million euros. This investment contributed to savings in the order of 3.5 million euros in what it comes to public spending in drugs and complementary diagnostic procedures. In the same year 1086 workplaces were dedicated directly to CTs and these studies were responsible for a global Gross Value Added of 72 million euros. For each euro invested it is estimated that there is a return of 1.98 euros, making this area one of the more profitable of the country.

In spite of this good economic values, Portugal does not take everything that it could from CTs. In fact, being the CTs one the main indicators of the interest in innovation and investigation in health, the reduction of the number of CT in Portugal shows how we are losing competitiveness in a progressive and alarming pace.

A recent study conducted in joint by Pwc and APIFARMA in 2013 gave a clear image of the actual panorama of CT in Portugal(33). According to this report, the number of CT submitted in Portugal from 2006 to 2012 fall an impressive 26%, going from 160 to 118 studies. Actually, in 2011 it was verified the lower number of CT registered since 2006, only 88 studies. Concerning authorized CT the number has gone from 147 (2006) to 99 (2012) having the lower number been reached in 2011 as well, 87 studies, a drop of 33%.

It is not easy to invert this trend. To increase Portugal's competitiveness in the enrollment of new CT some measures needs to be established. One of the things that are influencing the loss of competitiveness comparing with other European countries is the average time that a CT takes to be approved. This approval time lasts since the submission of the initial approval request and the reception of the last regulatory entity approval and in 2012 it was of an average of 70 days. The aggravating of this numbers is that these 70 days do not include the time that the hosting institution takes to approve a trial. If we add this time to the already more than 2 months it can rise to more than 6 months from average time to approve a CT.

Inefficiency and uncertainty clarification requests, absence of legal deadlines for approval of the financial contract, and a mandatory approval by the National Committee for Data Protection without legally stipulated deadlines also hurt Portugal's competitiveness. From 2009 to 2012 the average percentages for each phase of CT was of 2% for Phase 1 studies, 18% for Phase 2, 70% for Phase 3 and 10 % for Phase 4. This shows the importance of phase 3 studies in Portuguese clinical research.

This report also stated approximately 98-99% of CTs are held by international promoters and 94% of trials in Portugal are promoted by the Pharmaceutical industry and only 6% was held by academic institutions in the year of 2010, mainly due to the lack of legislation regulating and promoting academic research. This last indicator differs in great scale from countries like United Kingdom and Spain, where academic investigation represents something like 25% of the total studies.

Continuing to compare Portugal with other countries, in this case, with ones that present a similar number of inhabitants such has Austria, Belgium and Czech Republic we can observe that we are far below from the other countries as is shown in the table 2. These values were obtained by APIFARMA in a survey realized in 2009 that got information about CTs conducted by ten pharmaceuticals in Portugal and comparing them with the previously referred countries. This numbers is alarming since Portugal is losing money because the lower number of trials implies less money being applied in the country.

Table 2. Portuguese CTs expression compared with size equivalent countries (33)

Country	Number of active CTs	Number of planned sites	Planned patient recruitment	Investment (in millions of euros)
Portugal	147	461	3.917	58,755
Austria	188	596	5.602	97,530
Belgium	328	1.024	12.996	194,940
Czech Republic	218	967	15.433	231,495

Patient recruitment lack of efficiency is another factor that is slowing the entry of money in Portugal from CTs. According to another APIFARMA survey conducted from 2007 to

2011, in a universe of 443 trials, sensitively 14 million euros were lost due to failed patient recruitment.

Facing all of these indicators it's obvious that there is room to develop the efficiency of CTs in Portugal in order to get a better profit. There are some main obstacles that shall be faced in order to fulfil that: Politics and Strategy; Policy and Legislation; Organization and Infrastructure; Incentives and Training; Technology and information. The transposition of the current European Directive for CTs is seen as one of the more important factors to the lack of efficiency in this are in EU especially in some countries like is the case of Portugal. Promote communication between stakeholders and recognize the window of opportunity that was created by the last review of the UE legislative network in March 2014. A turnaround in this trend could bring a lot of benefits, especially financial, to Portugal such has:

- Contributing to the budget of the state through paid taxes.
- Providing alternative cost savings.
- Being an additional mechanism of remuneration to investigators.
- Creating employment opportunities with additional work for researchers and young physicians
- Raising economic stimuli for other supporting business.
- Giving improved access for patients to better treatments (a patient under a trial has a more intense monitoring than one that is out of any trial);
- Generating knowledge sharing and transfer of new technologies.

This panorama got me very excited to work in this area and I expect that with my work, I can somehow help to the evolution

2.6. Overall CT stages

To give a clearer idea of how a CT is conducted and which are the regular procedures since the idea of performing a CT until its end and presentation of its results I will give a brief description of it.

2.6.1. Feasibility assessment

The birth of any CT in a research center results of a sponsor, academic or from the industry, wishing to perform an investigation. At a national level, the sponsor evaluates

if is feasible to implement a trial according to the number and conditions of the centers that are willing to receive the trial.

After passed this general evaluation phase, it is checked the feasibility inside each center. During this process is checked if the site is adequate to receive a trial in terms of facilities as well as if it has an experienced and qualified staff depending on what the trial demands, if the site has access to a patient population that can be enrolled and if the healthcare professionals of the site are really interested in performing the study. Most of times, this involves a questionnaire to be filled by the PI with the help of the SC. As a part of this phase some meetings between the representatives of the sponsor and the PI and SC occur. The objective of these meetings normally are discussing the number of subjects that the site is willing to enroll, which barriers most likely will appear to this study and also the financial agreement is discussed. With an affirmative ending to all this conversations and procedures, the center becomes eligible to enter the study

After the assessment of feasibility, submission to the administration board and to the ethics committee has to be performed. If the trial is approved the center is eligible either in the point of view of the promoter as well as by the hosting institution.

2.6.2. Investigators meeting and Site Initiation Visit

The next step is performing a investigators meeting where there is a training on the study protocol and ICH-GCP (5) to all participants including CRA, SC, Investigators, medical monitors, quality assurance professionals and senior management.

After the investigators meeting, a study initiation visit is performed. During this visit, representatives from the sponsor come to explain in what consists the trial to the healthcare professional that will perform the study in the site. Any question that exists about the study design and procedures or any other detail shall be recalled in this meeting. After this meeting the enrollment of patients may begin.

2.6.3. Study phase

Before any patient is enrolled to the study, he must be informed about everything within the scope of the trial by one of the investigators of the study. At the same time a copy of the informed consent is delivered to the patient so he can read and be clarified about study procedures, study drug information, safety concerns, ethical and financial considerations between other matter in order to take a conscious decision about entering or not in the study. If he manifests his will in entering the study it is appointed

a visit with the PI in order to both sign the inform consent, indicating that the subject agrees to ponderously enter the trial. Once the Informed Consent is signed, the next step is scheduling the Screening Visit.

In the screening visit the patients is asked about him, familiar history and performs some exams in order to check if he fits all the inclusion and exclusion criteria. If he does fit the criteria, the patient advances to the baseline visit. In this phase if the trial is randomized with more than one arm in its study design, the patient is allocated to one of the treatment arms, which can be, depending on study design, a dosage of the study medication, an active comparator or a placebo.

After its randomization the patient enters the treatment period of the study which can last from a few months to some years depending on the application of drug that is being tested and on study design. For example normally medicines for chronic diseases need longer trials then the remaining and phase III trials are longer than phase II. In this treatment period regular visits to the site are performed in order to follow the patient looking for AEs, checking his willingness to continue in the trial, drug accountability and perform many other medical procedures considered in the study protocol. All the data collected in these visits shall be registered.

If the patient reaches the end of the trial he can enter in an open-label follow-up of the study or he can receive the drug by compassionate use if not entering a new study. The first situation is directed to people that where involved in blinded investigations. In the case of blinded CTs, after the investigation is over the subject may enter an extension phase in which he knows that he is taking the medicine. Normally patients opt on this when the previous results about the study medicine are good and there is a trend to believe it is really beneficial. Compassionate use is the usage of a still not marketed and authorized medicine. This program of prescription is dedicated for patients of the EU without a satisfactory authorized therapy to their disease and cannot enter a CT.

Sometimes, the patient may not reach the end of the study for any reason such as simply don’t want to be a part of the study anymore, stop fitting the study criteria, taking prohibited concomitant medication, a serious AE happening with causality attributed to the study drug or a female participant might become pregnant or the participant death. The patient safety is always in first place so if there is anything that can put its life in danger within the scope of the CT, he is immediately discontinued of the study.

The SC is present in every stage of this process being an essential member to guarantee that the study is well coordinated and documented and by helping the entire

research team. I had received training during my internship to be able to perform my activities in each of the phases as a SC. That training together with other experiences and projects will be referred below.

3. On-the-job training

During my internship my main focus of training and practise was in activities related with CTs coordination. Apart from this area of training I also had the chance to go through some monitoring activities, assist and participate in the preparation of an audit, develop systematic reviews, being familiarized with practical pharmacovigilance procedures and quality systems and have some extra theoretical training in diverse areas. I describe those activities below.

3.1. Disclaimer

Before I continue describing my internship activities I want to alert that being a part of a CIC I had to, in the beginning, sign a confidentiality agreement concerning the sensitive and confidential information that I would manage working as a SC trainee. Study protocol and investigator's brochure information along with the participant's data are some of the material that I cannot share. I can, anyway, share information that is of public access such as the trials names and general information about the trials and as well describe what I have learned during my training as SC.

3.2. Timeline of my internship

During my internship which lasted between September 2013 and June 2014, I spent most of my time assisting has a SC. Actually, that happened because my biggest objective coming to this internship was to be in contact with clinical studies coordination. When I have arrived to the center in September 2013 I was introduced to the CTs that were part of the CIC set of active studies. From 9th to 20th December, 2014 I was in UFLVT and I was trained on the usual processes taken from the moment of the receiving of a notification to its imputation of causality and which consequences it may have. At the same time I had the possibility to study the UFLVT quality system. That was very useful because it was the first time that I contacted with a complex quality system in a professional environment. After these 2 weeks I returned to the CIC where continued my training as SC. In March I was challenged to start performing some research in order to do a systematic revision. I took part of 3 investigations and in one of them I was the PI. In the latest months of my internship together with the support that I gave in all the clinical center studies I was assigned to an Alnylam CT in *Familial* Amyloid Polyneuropathy (FAP) named ALN-TTR02-003 with the role of SC.

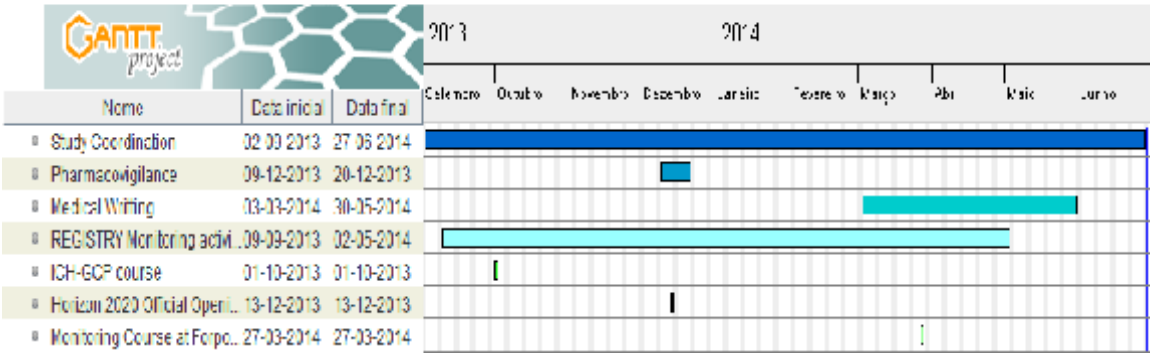

Figure 4 - Timeline of my internship

3.3. Arrival at the internship organization

In my first day of internship I had a meeting with my internship supervisor Professor Joaquim Ferreira in order to define in which area of the UFC I would primary be allocated to. Since my main objective coming into to the internship was to have training in study coordination, Professor Joaquim Ferreira suggested that I stayed mainly at CIC. In my first week there, I spent most of my time getting familiarized with the structure and operations of the center and with my colleagues of the research team in order to be able to cooperate with the rest of the team, once the SC role is in the center of the all CT related activities. The group is composed by professionals with different backgrounds and different roles within the team. It the center collaborates at full time two SCs, Ana Noronha and Maria Finisterra and a laboratory technician, Antonieta Alves Apart from those, also a group of physicians, which are the studies' investigators, psychologists, study nurses and pharmacists, also give support to the CIC CT.

3.4. Study of Regulatory Literature

Before I started to get involved in CTs procedures I had to restudy the literature that regulates and gives orientation to clinical investigation. The bibliography regulatory documentation that I described in Subchapter 2.3. "CT Regulatory Framework" was the main support to my training in terms of general knowledge about regulatory considerations.

3.5. CT Essential Documents

After having a close knowledge of the regulatory documents in which clinical investigation resides its orientation my theoretical training was yet not over. Before I got in direct contact with the different CTs and running its related procedures, I had training about them through the study of its documents and procedures. I had contact with the CT Protocol, Informed Consent Form, Investigational Product, Subject's diaries, AE and Serious Adverse Event (SAE) reports, Investigator Site File (ISF), CRF, Source Documents (SD), Monitoring requirements and Central Laboratory. Details about each of these matters will be later described. This early theoretical training was very important on helping me to perform my job properly in the different trials.

3.6. Study Coordination Specific Training

Concerning my specific activities in study coordination I was introduced by my colleagues of CIC to the procedures that I would have to perform as a SC across the different phases of each CT. I participated In the processes of more than 10 CTs and in five OSs. Each of them had different protocols with different procedures to be followed and executed. In spite of that most of the things that a did across the different studies can be matched. I will describe the training that I had and the tasks that I developed during this year of internship, which are intimately related to the activity of a SC. For that I will divide this description by the different CT stages as explained in subchapter 2.6.

3.6.1. Attending feasibility and investigators meetings

During my internship I had the opportunity to assist to the feasibility assessment of CIC for 3 different CTs. I was present during some meetings between CRAs and other representatives from the promoter and members of the CIC, namely each CT PI and the SCs. I had the chance to get contact with the matters that are discussed during this meeting such as the financial agreement, some doubt clarification about the study requirements, the definition of how many patients would be included and the discussion of some barriers that predictably may appear during that CT. I was instructed about what are some of the SCs tasks during this phase that are specially directed to the interaction between the sponsor and the administration board and the ethics committee and by obtaining and submitting all the necessary documentation prior to the acceptance of a CT in CIC.

I did not have the chance of attending to any investigators meeting but my colleagues SCs shared with me the importance of the presence in the reunion of either the study PI and the SC once in these meetings they are trained on the protocol and procedures and important comments with the objective of improve the CT design or processes are made.

3.6.2. Site initiation visit

I had the opportunity to attend to site initiation visits from three different trials. The importance of these meeting has already been referred in subchapter 2.6.2. After attending to these meetings, normally I would together with my colleagues SC and the sponsor CRA gathering a list of necessary documents for being signed such has the delegation log, the study initiation visit signature page or CVs not yet delivered by the professionals involved in the referred CTs.

3.6.3. Online and by telephone trainings

Before it is considered that a SC or any other participant in a CT is enabled for doing a procedure, he has to go through training. This can be performed by watching an online training which normally as a final evaluation to assess the professional's capability to do the procedures or by attending to an interactive teleconference in which is explained by a promoter representative everything about the tasks delegated in each person. I had the possibility to view or assist by several times to these trainings or teleconferences. These trainings included matters like the Electronic Case Report Form (e-CRF), ICH-GCPs (5), IVRS/IWRS, samples shipment, ECGs and VS and the screening and randomization process.

3.6.4. Patients visits

After the site initiation visit patients may start to be included. The activities in which I was trained as a SC during this phase can be divided on the ones that are performed before, during or after the subjects' visits as is explained below.

3.6.4.1. Prior to the visits

The first thing to do in order to prepare a study visit is scheduling it with a patient. I was trained on how to contact with patients depending on their limitations in order of clearly transmitting all the needed information.

When the visit day was coming I would look to the study flowcharts in order to see which procedures would have to be performed. In some studies I also prepared my own checklists and worksheets in order to better organize the upcoming study visit. This was important because each study visit has an order of procedures that shall be followed and in addition to that of them some can take a lot of time if not planned properly. Elaborating these checklists can make easier the investigators and raters job and at the same time reduce the duration of the consults avoiding a high burnout for the patients.

I would then gather and prepare all the needed material. In this material is included patient's medical record, CRF/Patient's binder, study kits, IVRS worksheets, EGC readers, patient's diaries, questionnaires and scales, form to record VS, pharmacy prescription form, sphygmomanometer and thermometers, etc. It was my function together with the others SCs to prepare everything in order that when the study participants arrived for the visit, the persons responsible for performing the procedures (physicians, psychologists or laboratory technician) had every logistic requirement available.

One of the important points that we always had to be aware of was if there was a need for medication in each visit. Prior to the visits in which was scheduled to provide medication to the study patients, together with the other SCs I had to send to the pharmacy the request of the necessary study medication according to the protocol. I was taught how to develop this process by getting the prescription documents from study files and asking the PI to sign in in order to send it to the pharmacy. This process shall be performed in an adequate time, so that is guaranteed that no delays happen with the trial medication delivery to patients. In some studies it was required a medication request to the IVRS which was normally done by telephone. In order to keep a good communication with the pharmacy, additionally to formal medication request in the day before of the visit, every Friday I would send to the pharmacy a calendar with the schedule of all the visits with medication that would happen in the CIC.

In some visits there were some procedures such as the infusion of IV medication or the application of other injectable medication which required the addition of a nurse

member to the staff. Whenever there was a need for a nurse support I had to communicate it to the nurse team or individual with antecedence and ensure that training about the procedures contained in the visit would be provided to the professional(s).

Every time that according to the study protocol or by investigator's/sponsor's indication a local laboratory exam or any other test in any medical specialty such as neurology, cardiology or ophthalmology were necessary, I had to request those exams prior to the study visit.

If any of these activities failed there could be some problems during the patients' visits so it was very important to carry this phase of planning and visit preparation with special seriousness.

3.6.4.2. During the visits

During screening visits, I helped the PI in the Informed Consent Process especially in the clarification of the CTs specificities to the subjects. Then the physician provided the medical and scientific information and evaluations required while I was more responsible with guaranteeing all the requested logistic information that the patients needed including information about how their transportation from home to the CIC would be carried, where would he have to go to perform the evaluations that were not perform inside the CIC and the clarification of how any monetary spending caused by the participation in the CT would be reimbursed.

During the rest of the study patient participation I assisted in some procedures directly with the patients. I received training about how to work with an EGC machine and how these exams are performed and how their results are sent to central reading for a further clinical report emission. Under other SC supervision I had the chance to perform these tasks, paraphrasing performing ECGs exams, sending its reports to central reading and archiving its impressed registries. I also received training in measuring VS such as blood pressure, pulse, temperature and respiratory rate. Additionally, I assisted the patients in completing some questionnaires that did not require the presence of a physician or a psychologist. My assistance was especially useful in helping patients with disabilities in terms of reading or writing, text comprehension or vision problems. Having this close contact with the patients allowed me to get more into each study and its related disease by being able to contact with the patients limitations and needs.

In some of the patients' visits it was part of the protocol, the collection of biological samples such as blood and urine to perform after the required laboratory exams. I

received training on the tasks related with laboratory procedures as stated in the laboratory manual of each CT. This training was essentially given by the SCs and the laboratory technician of CIC. I learned and practiced on how to prepare the necessary kits for each of the study visits and how to handle them. I also got to learn how to work with a centrifuge and how to process and ship the different samples. Some samples, normally the ones conditioned at air temperature, were by norm sent in the very same day of the collection to the lab. Regarding samples condition at negative temperatures, some of the times were send in the same day but could also be sent in other day depending on the laboratory protocol indications. When there was a need to keep this frozen samples we would store them in a refrigerated at a controlled temperature and at the time of their shipment dry ice and a specific transport box had to be available. For request the samples shipment we had to phone, e-mail or fax the carrier defined by the promoter who would pick up them. Additionally we would have to fill a request form to be sent together with the samples and whenever new materials such as laboratory kits or transport boxes were needed we had to contact the laboratory for a re-supply of it.

3.6.4.3. After the visits

After the patients visits I checked if all source documents were signed and dated properly. Then I would transfer all gathered information from source documents (ex. Subject clinical file, ECGs, laboratory results, questionnaires, etc.) into the Study CRF. CRFs exist both in paper or digital format depending on study. With the supervision of my colleagues SCs I learned how to assess and enter data in the different CRFs, how to answer queries and on how to make ICH-GCP (5) entry corrections on paper CRFs. Normally each study uses a different CRF platform and template which implies that we are familiarized with all kinds of systems. Additionally, I was aware about the importance of keeping confidentiality on CRFs completions. If an ECG was performed during the visit I would sent its registry to central lab for evaluation and all material used had to be archived correctly on the patient's folder. Checking the CIC stock of laboratory material was always a must-do task after every visit.

Apart from these activities directly related with the study visits, either with their preparation, development or data handle, through my internship I can also refer some other tasks in which I was trained as follows stated below.

3.6.5. Study closeout visit

After the last CIC included patient in any trial finishes his last visit, the study in concluded. After this a closeout visit is scheduled between the Sponsor/CRA and SC/PI. By this appointment all CRFs must be filled and unresolved queries answered. Prior to this visit, apart from those tasks, I also helped on providing all the info that was presumed to be necessary as the temperature logs and the signatures of team members related to their study activity stop dates. The remaining study documents are kept in the study cabinet until sponsor's agreement for the archiving of those documents in the dead archive.

3.6.6. Archiving of CT's documents

According to the Portuguese law (20), the documents referred as essential shall be archived for a minimum period of 5 years after the study it's over. In spite of that, normally study documents are kept for 15 years due to the instructions of ICH-GCP(5). During my internship I helped in the archiving of two CTs essential documents. These documents were sent to the Central Clinical Archive in closed boxes after the study Sponsor's agreement.

3.6.7. Permanent contact with CRA

A very important part of the SC's activity is contacting with the studies promoter or the Contract Research Associate (CRA) that represent the promoter. Normally that contact is made through the CRA either by phone and e-mails or by in-site visits. The CRA is the nominated representative of the interests of the promoter in a CT and so he monitors the CT ensuring that all the procedures related with the study remain in compliance with the study protocol and ICH-GCP(5). As a SC trainee I had contact with CRAs specialty through the training that I had in answering queries, scheduling of monitoring visits, notification of AE, alert about needing of stock refill and by providing and receiving all the documents and information related with the CT.

3.7. The Alnylam Trial

During my internship, included in my training as SC, I got especially involved with some diseases. My main focus was on Familial Amyloid Polyneuropathy and its related trials. One of this was a study sponsored by Alnylam called ALN-TTR02-003. In this trial, ALN-TTR02, a molecule intended for the treatment of Transthyretin-Mediated

Amyloidosis(ATTR), administered intravenously had the purpose of evaluating safety of tolerability of its long-term dosing in patients with ATTR who have already been treated with this investigational product. This is an open-label extension of the trial ALN-TTR02-002. Participants had to be between 18 and 85 years old, have participated in the study ALN-TTR02-002 and have an adequate Kamofsky performance status, liver function and renal function. Being pregnant or nursing in the case of women, having a liver transplant, having a New York Association heart failure classification bigger than two or having an unstable angina or uncontrolled cardiac arrhythmia were exclusion criteria.

Because of my close contribution on the study in the context of my training in study coordination, the CRO responsible for the trial decided to include me in this CT with the functions of SC. This gave me a lot more independence, although I always had the help of Ana Noronha and Maria Finisterra. I was in close contact with all the intervenient of this CT as is the normal SC task providing all logistical support and knowledge about the study protocol.

I collaborated together with the colleagues of other study sites and with the study CRA elaborating a checklist that would help the study staff with each visit procedures. This was a complex trial in which each visit had a elevated quantity of assessments so this checklist revealed very important, working as a source document as well as guidance for the visit line of actions. Additionally I had to prepare the study's medical appointments, carry the needed equipment, contact with the CRA either by phone or in in-site monitoring procedures, contact patients in order to alert them when the day of the consult was approaching, contact with the pharmacy warning them of the need for a medication in a specific day, etc. Ultimately, with this CT, I ended up facing my first official challenge of putting into practise everything that I have learnt in the other studies

3.8. Other Activities

In addition to my training as a SC I performed other activities during my internship. Activities that include monitoring, audits, group meetings and pharmacovigilance training as reported in the following section.

3.8.1. European Huntington's Disease Network (REGISTRY)

At the same time that I was training in study coordination, I got involved since the beginning of the internship in a prospective cohort study of the REGISTRY. This study is a multi-center, multi-national OS without experimental treatment being a part of a worldwide network working towards treatments for HD. The hospital where is physically located my center of internship, CHLN, E.P.E. – HSM is the Portuguese language coordinator(34).

Working on this trial at the same time I was trained in Study Coordination and in Monitoring. Study coordination activities were develop in our site and my tasks were to prepare visits' logistics such as copies of the evaluation scales, either neuropsychological or motor, labelling laboratory kits and preparing samples shipment. Additionally I distributed questionnaires to patients helping the ones that had any difficulties in comprehension, reading or writing on them. After the visits I would have to enter data in the e-CRF and archive all the questionnaires and scales performed during the visits in the patient file.

Regarding the monitoring activities, conjunctly with my colleague responsible for the REGISTRY I performed some online and onsite Monitoring visits of the study e-CRF. In these last, made for ensure the high quality trial conduction. In these visits the following activities such as reviewing the ISF and listing what's missing, checking if ICF's were correctly signed and dated, solving queries in presence of the site team, checking the source documents and the e-CRF and help the study team when they request it.

After these visits, I had the opportunity to observe my colleague elaborating a Monitoring Report Site Visit, where a follow-up of the visit is written and included information such as the number of participants recruited by the center, number of participants monitored, ICF incomplete and missing, protocol deviations, adherence to study visit schedule, correction of previous issues pending and queries to be solved. This report is then sent to the EHDN international coordinator team to be reviewed and an follow-up e-mail is also sent, in this case to the visited site to describe what was done and what shall be done by the site to improve their efficiency and mitigate its issues.

The process that we did in these centers was also performed by colleagues from Spain that were the professionals responsible for monitoring CHLN, E.P.E. – HSM. We had to try to answer to the most possible number of queries online in order to facilitate their job of online monitoring and reduce the needs of in-site monitoring. When those in-site

monitoring visits were actually demanding, we prepare the center and the documents for them to make the entire visit easier either for us in site and for the monitors.

3.8.2. Audit

From April 28th to April 30th, the CIC received an audit related with one of its trial. Before the audit a CRA was sent by the CRO responsible for that study to together with the study center staff, prepare the study center in order to receive the auditor. This auditor was belonging to the study sponsor and had a very meticulous approach to the study center and to all the study documentation. The objective of the audit was to check every little detail in the study center or study documentation that was not in compliance with the study protocol or ICH-GCPs(5). This audit was stress and laborious to all of the study staff members once we had to intensively prepare the visit to assure that everything would be ready to receive the auditor and to answer and provide him anything that he would request. At the end of the visit, a closing meeting happened where it was discussed the principal findings of the audit by the auditor, the PI and the rest of the study center staff team.

3.8.3. Journal Club

Once a week, by convention at Wednesday by 8 am, the members of the CIC and the CPU teams join the CIC "Journal Club". In these meetings headed by Dr. Miguel Coelho, members previously chosen present a recent article in the area of neurology and neurosciences. After the presentation, there is a little discussion about the study's design and findings, its usefulness to clinical research and therapeutics and if a possible similar investigation could be performed by the center's team or if between the study findings some conclusions could be helpful for the CIC team research work. Apart from this component of articles presentation, these meetings also were useful for a share of information between the team members about their daily activities and potential needs for collaboration.

3.8.4. CPU meetings

Most of Wednesdays afternoon was marked by a meeting held on the LCPT. These meetings allowed team members to present projects in which they were working on. This was useful in order that all team members were constantly actualized in what each of us was working on allowing for cooperation and ideas discussion about the already

in development or potential new projects. These meetings started in mid-November when all the members of the team introduced themselves and their area of work. This mutual presentation would reveal very helpful for further cooperative work.

3.8.5. Pharmacovigilance

During the days that I spent in the UFLVT I learnt some procedures that integrate the functions of a pharmaceutical working in this unit. I learnt how to process the received spontaneous notifications or AEs to drugs and how to proceed when it comes to follow up these notifications and close them. I learnt also how alert signs are generated and why and that a causality imputation is done by a clinician. I had to learn as well during this time in the UFLVT how the unit quality system is organized by studying their quality system manual.

3.9. Courses

During the time I was in my internship I had the possibility to attend and receive some extra training which could help me improving my skills and knowledge in areas such as ICH-GCP(5), monitoring and entrepreneurship as referred below.

3.9.1. ICH-GCP course

My internship was still on my first month and I already had the notion that the CTs world was all around ICH-GCP(5) so in On October 1st, 2013, I had the opportunity to attend a ICH-GCP(5) workshop, headed by Doctor Ingrid Klinman from the PharmaTrain Initiative at UA. This activity was part of the inauguration session of the 2013 year of the Training Programme in Pharmaceutical Medicine.

In this session it was presented a historical contextualization for the appearance of ICH-GCP(5), with references to the Nuremberg Code and the Helsinki Declaration, and the modifications that these guidelines suffered during time. Additionally practical cases were approached such as patient compliance, requirement of informed consent and the specific case of minors and other vulnerable people. This was a very interactive session with space for a lot of discussion in special in themes related with ethical dilemmas.

3.9.2. Monitoring Course at Forpoint

On March 23rd I attended a Monitoring Course in CTs in the Perspective of the CRA at the Keypoint facilities. This training was important to give me a view of what are the CRA tasks, difficulties and required skills in order to have a better efficiency on working together with the monitors.

3.9.3. Horizon 2020 Official Opening Session

On 13th December I had the chance to attend to the Horizon 2020 program opening session. This is a program sponsored by the EU and promotes research and innovation having for that available a total of 77 billion euros for support to investigation. Attending this meeting made me aware to the opportunities of financial funding to investigation and that excellence and entrepreneurship can be supported and rewarded.

4. Systematic Reviews and Medical Writing

During my internship I got some contact with systematic reviews, especially on which phases should be considered when planning this kind of investigation, what research strategies should be followed and which databases can be used for search information such as PubMed and Medline. Regarding my medical writing activities I had the possibility to work in three different systematic reviews with the following themes:

- The Study Coordinator activity
- Clinical Trial monitoring – where do we stand? A systematic review
- What can we say about clinical research networks?

These papers appeared after a proposal from Professor Joaquim Ferreira, who challenged me and my trainee colleagues Marcio Barra and Ana Salgueiro to write a paper on a matter related to CT.

We decided to collaborate in the elaboration of the three papers. I ended up being the PI in “The SC activity” paper and a secondary investigator in the other two. More detailed explanations about the theme of each of the papers are in the sections below. These three papers are at the moment in a pre-submission phase.

4.1. The Study Coordinator activity

This research theme was chosen due to the increasing of the number of studies by study site and the higher exigencies of safety and efficacy on CTs what imply that all of these investigations are very well controlled as well as the study sites where they are carried. All the procedures must be in compliance with study protocols and ICH-GCP rules.

This makes very important having a qualified person coordinating the study center in order to provide an excellent support to experienced and multifaceted teams that can include physicians, psychologists, physiotherapists, pharmaceuticals, nurses and statisticians. This has the objective of speeding up most of the processes facilitating the work of not only all the other members of the study site team but also from other professionals such as PIs or auditing teams.

This review intended to compile the available information about the legal environment regulating the CRC position, primary ethical challenges, CRCs’ main activities and

required skills and the debate of whether the CRC position should be occupied only by nurses.

4.2. Clinical Trial monitoring – where do we stand? A systematic review

The PI of this paper is Márcio Barra. We decided over this theme because of the current debate of on-site monitoring versus the newer concept of centralized monitoring. On-site monitoring is where the CRA is assigned to monitor a clinical or observational trial in a study centre or group of study centres carrying an in-person evaluation at the sites. Centralized monitoring is more technology reliant, where the CRA, or any assigned sponsor personnel, conducts a remote evaluation of the study centre. Through this investigation is assessed the pro and con of both of the monitoring strategies

4.3. What can we say about clinical research networks?

The PI of this paper is Ana Salgueiro. This paper surged in the following of the verification that the current model of research is no longer productive and that the cost-effectiveness relation is doubtful. Due to that there is a decrease in the development of innovative therapeutics and an R&D process crisis. Some changes need to take place among the research community so the attrition rate can be passed and success reached. One of the strategies is going from small and with lack of communication groups of investigation to networks of researchers that together can innovate the process of research, optimize resources and share data. Presently, we can find well-established and connected clinical research units, named Clinical Research Networks. In this paper these networks and their strategies for success are reviewed.

5. Discussion

In order for a new medicine being released to the market it needs to go through a set of studies to obtain information and evidence on its safety and efficacy. Those studies are CTs. My internship was mainly focus on CTs and OSs, particularly on its coordination. Together with the coordination activities I performed other activities, having set a group of objectives in the early stage of my training that I would like to accomplish during the time I would spend in this institution.

Since the time I arrived to the centre have already passed 10 months. During this time I performed several different activities and acquired a relevant combination of knowledge and experience. What was written in this report cannot rightfully reflect all that I have passed during my internship due to all the particular moments that have composed it. What I try is to give a view of the more important things that I retain from this first contact with the professional environment.

Performing my training in CIC inserted in a hospital as revealed being very profitable for me because of all the different kind of patients and healthcare professionals that I have met and contacted with. Since the beginning of the internship, this gave me a special sensibility regarding how to interact with these different persons depending on their education, literacy and mental health since is not the same thing to communicate with a clinician or with an AD patient for example. This kind of personal involvement gave me a more widespread view of the different persons that I might have to contact during the internship and prepared me for being a more versatile professional.

The persons working both at CPU, UFLVT and at CIC are all very serious and qualified professionals, always in a constant effort to perform their work with the best efficiency. This makes these institutions very successful in their activity. All of these professionals, including clinicians, SC, statisticians, psychologists, nurses contributed to my training by always being available to help and guide me whenever I needed.

CIC, which is the institution where I have spent more time, has a team that is very focused in having increased numbers of patient recruitment while keeping quality of assistance provided in an high standard. With all this effort is not to wonder the feedback of satisfaction that is normally received from patients entering in CTs at CIC. This is very important in CT activity since, concerning ethics, the wellbeing and the interests of participants are always the main aspect when conducting investigations.

CIC assumes itself has one of the Portuguese centres with the highest recruitment rate having in opposition a low rate of study withdrawals. Since its formation in 1999,

sensitively 140 CTs or OBs have already been performed in this centre, demonstrating its importance in the Portuguese CT frame. It was very positive for me to train at such well provided and recognized institution.

This numbers express how organized, ambitious and dedicated person working in CIC really are. Skills like being a good communicator and scientifically precise are some of the qualities that are shared by all of these professionals. This is fundamental in the area of clinical investigation since this is a very demanding area especially due to the entire regulatory framework that surrounds this activity.

Some guidance and ethics documents were already referred in this report including the Nuremberg Code, the Helsinki Declaration, the ICH-GCPs, Directive 2001/20/CE, Directive 2005/28/CE and Directive 95/46/CE. These are the basis of CTs regulation and soon after I arrived to CIC I got in close contact with these. I got an extensive training on CT ethical consideration in my first weeks of internship. This process was softened by the fact that during my training I had already have a good background regarding ethics matters.

My Bachelor in Biomedical Sciences and my first year of MPB were the base for this internship providing me with knowledge and interest in the area of CTs. This was fundamental for making me quickly feeling inserted in this environment. I had already an extensive training on CTs either by knowing their different phases characteristics, being aware of which are the regulatory authorities and the regulatory literature that are behind CT framework and knowing how, presently, the investigation investment and interest looks like in Portugal and in the rest of the world. Out of university and coming to the internship I also had already some background information about the institution where I was coming to, but only when I arrived I realized how complex was its structure and its mission. My luck was the great group that worked with me and explained me how are divided the different groups of CPU and what activities each one of them performs.

After having received my early training on guidelines and on the centre's structure and mission I was ready to start my training in order to follow the objectives that I set for this internship.

My primary objective was to receive training as SC. I consider that this objective was fully accomplished. I was able to develop my knowledge and experience in almost all the tasks that are delegated to this professional. The most outstanding point that I feel that I developed were my organization skills. I when arrived to the centre I was not a

very methodical person and in the first weeks was hard for me to deal with so much amount of work and responsibilities inherent to the job of SC. As the time was running by I started to figure out that I had to start to get a method to be able to do all the word that I had in my charge. So I had to get more organized and plan with time all the activities that I have for the following days keeping always the ability to deal with not expected situations. A SC always has to be focus in his activity in order to quickly detect any fail in the compliance with the running studies protocol and with ICH-GPC. This constant monitoring is important to prevent major deviations that can lead to problems regarding the study patients, or the study sponsor. I felt that the background training from either my Bachelor and Master Degrees were extremely important in order to develop my training as SC more efficiently and I had the secure feeling that I applied the knowledge that I already had during this year.

I had contact with several CTs and OSs but the one that marked me the most was the Alnylam study ALN-TTR02-003 in which I was officially included as a SC. This allowed me to perform more freely some managing and monitoring activities and was also very important by becoming the first CT that I could actually include in my curriculum vitae in spite of having taken an active part in a lot more trials. Regarding these other trial they were all very important for me, mainly due to its variety of study designs and procedures, from different sponsors, which challenged me to have to separate in my mind the different processes in order to all the tasks in compliance with each trial's protocol. Among these trials a big set of target disease can be identified. The more common were PD, AD, FAP, HD, Dystonia, Spasticity, Multiple Sclerosis and Epilepsy. Having contact with all of these diseases refreshed me my knowledge about such neurologic pathologies that I had theoretical training about in my Bachelors in Biomedical Sciences. I felt that my background knowledge was really useful either for me, either for my colleagues from CIC.

I had to work with a lot of equipment which I did never worked with, such as computer specific programs for each trial, namely the different e-CRFs platforms, ECG machines and centrifuges. This was also fascinating for me since I had the opportunity to deal with some tools that were not of familiar to me and that I had to get used to. Online and by telephone trainings were also very important helping me using this new tools. These trainings are obligatory for the intervenient in each trial and apart from teaching how to work with this equipment also there are trainings that refers to ICH-GCP, biological samples process and shipment, CTs' documents archiving and study design and protocol considerations.

I also pointed the objective of get in contact with the CIC quotidian, its management and the activities that there are performed. I was able to realize that in general dealing with the centre's CTs and OSs predominate in the healthcare professionals' daily tasks. In spite of that, other groups or persons from the CHLN-HSM ´frequently contact with the CIC personal to ask for information and request for services such has asking for biological samples collection and shipment, I feel that I developed some managing skills working on CIC since a SC has to be the glue guy inside a clinical research team, providing to the other professionals whatever they need to perform their activities. This is even more highlighted due to the fact that these professionals have so much different backgrounds and roles inside CIC team.

Having the possibility of working with such a different group of professionals I set the objective of get some knowledge about their areas in order to make me a better professional. This was a little bit ambitious since all the activities are pretty different, specialized and dependent of each one background. In spite of that, I had the chance to attend to some clinicians consults and treatments, I saw the laboratory technician collecting biologic samples and nurses performing their nursing activities. I also contacted with statisticians and medical writer and got some notions about their areas and what are their tasks and, finally, I was pretty much in touch with the pharmacy colleagues. This elucidated me of how hard is to manage all the supply, storage and delivery of medication and all the bureaucratic procedures that are related with their daily activity.

Before coming into this internship I was in doubt of if I either wanted to have a SC training or a CRA training. Having the possibility to interact by several times with CRAs was very gratifying and useful because I had, as I wanted from the beginning, to understand what are the CRA's main activities and what is their overall importance in the clinical investigation framework. I witnessed how important their hard work is for keeping the studies protocol compliance and active collaboration with study sites. I got in really close contact with some CRAs that explained me their day to day tasks, how much time they spent on central-based monitoring and on in-site monitoring and what they do on each situation. I had the possibility to put into practise these teachings about monitoring in the frame of REGISTRY. In this OS apart from the coordination of the CHLN-HSM centre I monitored together with my colleague responsible for this study Maria Finisterra, either by web monitoring and by in-site monitoring in the other Portuguese centres. I can consider that besides study coordination, monitoring activities were the ones in which I got more prepared in the end of my internship.

As referred in this report, an audit was performed by a study sponsor to CIC. This was very useful for my training since I had my first contact with any auditing activity. It was important for me to understand that even when a research team has the idea that is doing is job one hundred percent in compliance with study protocol and ICH-GCP there may always be found some discrepancy and auditing actions are the best situations to filter those little or major deviations in order to a personal and team improvement.

The time that I spent doing scientific review and writing activities during the last months of my internship revealed very important to improve my skills in these areas. I got some train in systematic reviews in my contact with my colleagues at CPU that are responsible for these investigations and then I was able to put it into practise with the 3 systematic reviews in which I was involved together with my two colleagues trainees Ana Salgueiro and Márcio Barra. I got to know some processes like the OVID searches and what strategies to follow ina systematic search frame. Then I got to write about this reviews and its result is now in a pre-submission process. These activities were very interesting from scientific and skill enrichment point of view but were not the fields in which I felt more comfortable and motivated. By a large margin I preferred SC and monitoring activities.

I also was for some time in touch with the activities performed at UFLVT. This was really important to have a general knowledge about pharmacovigilance activities performed in a specialized unit. The processes of adverse events notification reception and its path until a possible causality imputation were shown and explained to me although I did not have the possibility to be an active part of this procedure and I limited to observe. Pharmacovigilance was not and is not my main interest area in what is related with medicines but I feel that having this more close perspective of the job done by these colleagues made me a better professional.

The group meetings that we had scheduled every Wednesdays, either the Journal Club or the CPU meetings, where very important in order to strengthen our team work and our knowledge about what each of our colleagues was doing. This is a very important example for me since in my opinion teamwork is the base for any activity, specially a centre where there is a multidisciplinary team with different backgrounds and interests where communication is a fundamental point in order to achieve efficiency. Journal Club was also important in giving me more specific knowledge about Neurology since recent scientific findings and publications where presented there by the different members of the team to set the tone for our own team new investigations and to share new and useful knowledge.

The trainings that I attended out of my internship environment, namely the ICH-GCP course, the Monitoring Course at Forpoint and the presence at the Horizon 2020 Official Opening Session where a very good complementary tools for my training since I could develop my knowledge on GCP guidelines, monitoring procedures and fostering my entrepreneurship spirit.

6. Conclusion

Being able to spend my internship in a area that compiles some of my biggest fields of interest, healthcare and investigational, was very rewarding and useful. Everything that I've learn make this experience unique and I get to the end of this year with the sensation that almost everything that I have proposed myself in the beginning of this journey was accomplished.

The place where I trained, CPU, particularly the CIC group made me feel comfortable from day one, which was one of the cornerstones to making this year become one of the most enriching ones of my academic life.

I have set some objectives coming to this internship. I received an extensive and efficient training as a SC as I feel that I accomplished almost completely all the objectives that I proposed to reach. There are only a few things that I think I could have done which I didn't. I would like to have been more in touch with statistician, since I think that its activity is very important in CT framework. I did not have the enough availability to spend more time getting to know their work. That happened due to the really time taking activity that being a SC is. I hope to compensate this low point with some future training in this area.

The same works with my medical writing skills. I had the possibility to have some theoretical training and putting it into practise with the revision report that I've made together with my colleagues SC trainee. Although not being my main area of interest I think is important for my professional future to have more training on my writing skills.

During the internhip and specially looking back at it, I realize how important my background training was to make easier the adaptation to the professional environment where I trained.

Working in a teamwork environment was very gratifying since for all my young life I got used to play in team especially due to my sportsman background. I really liked to fit into a team where everybody paddles to the same objective of improving investigation and providing the best treatments and care to patients.

This is very important working in the CT area because our main goal is based on the belief that our studies and activity will in the future enable better treatments to patients.

Besides working with our team, we also have to collaborate with other professionals such as the already reffered CRAs. My contact with them was so enriching as I was

able to watch and learn what are their main functions as I proposed in the beginning of the internship.

Being in close contact to the patients and witnissing their difficulties, thoughts and feelings makes us even more compromised with this objective of improving our effort to reach better treatments and every sign of improvement in these patients are victories for us.

I retain that as a SC there is an inherent responsibility concerning the CTs conduction in a clinical site environment. SC are keystones on the development of clinical investigations. I realized it during my internship since I observed that sites that does not count with this type of professional cannot keep such high levels of efficiency and safety when compared with clinical investigation centres is a SC. This happens because there is a lack of a person that fully dedicates his professional experience to managing and organizing every tasks and obligations concerning the clinical trials performed in its site.

In spite of that, a SC is nothing without all the other healthcare professionals that work inside the clinical site. This way, the most important lesson to keep in my opinion is that teamwork and a very well balanced and defined tasks delegation based on each professional knowledge and qualifications is essential. Only this way there is a high efficiency on the overall provided services of a clinical site.

Looking back I can notice that this was a very profitable experience, that was only possible thanks to the professionals that collaborated with me and to the background that I got during my Bachelors and Master's Degree. Looking into the future I hope that I can build up my career in the area of clinical trials as I would like to remain connected with these activities of study coordination a clinical research monitoring for the next times.

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