Universidade de Aveiro | Departamento de Ciências Médicas
2015/2016

NUNO MIGUEL DIAS ALMEIDA

ESTÁGIO CURRICULAR NUMA UNIDADE DE INVESTIGAÇÃO CLÍNICA

CURRICULAR INTERNSHIP IN A CLINICAL RESEARCH UNIT

Universidade de Aveiro | Departamento de Ciências Médicas
2015/2016

NUNO MIGUEL DIAS ALMEIDA

ESTÁGIO CURRICULAR NUMA UNIDADE DE INVESTIGAÇÃO CLÍNICA

CURRICULAR INTERNSHIP IN A CLINICAL RESEARCH UNIT

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 Joaquim Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa, e do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro.

Dedico este trabalho a todos os que passaram por mim
e que contribuíram para o meu percurso académico.
Dedico à família e aos amigos, por serem os meus
constantes pilares e por darem sentido à minha vida.

o júri

presidente	Doutor Bruno Miguel Alves Fernandes do Gago Professor Auxiliar Convidado, Universidade de Aveiro
vogal - arguente	Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta, Universidade de Aveiro
vogal - orientador	Professor Doutor José Carlos Fontes das Neves Lopes Professor Auxiliar, Universidade de Aveiro

agradecimentos

Ao Professor Doutor Joaquim Ferreira, diretor do Laboratório de Farmacologia Clínica e Terapêutica, pela oportunidade que me foi dada de estagiar e aprender num ambiente multidisciplinar e dinâmico.

Ao Professor Doutor José Carlos Lopes pelas suas palavras sábias e pelos seus conselhos, não só em relação ao relatório de estágio, mas também em relação à vida profissional.

Ao Professor Doutor Luís Almeida e ao Professor Bruno Gago, por criarem um mestrado de excelência e pela oportunidade de fazer parte do mesmo. Agradeço também pelo conhecimento transmitido e pela disponibilidade de auxílio durante estes dois últimos anos.

Aos meus pais, que sempre apostaram e acreditaram em mim, que me deram tudo o que podiam para poder ir semrpe mais longe. A eles devo eterna gratidão por tudo aquilo que consegui no passado e por tudo o que conseguir no futuro.

À minha irmã, que sempre foi como uma segunda mãe para mim. Posso dizer que agradeço pela sua insistência para ter um “mano”. Sempre acreditou em mim e me deu forças para continuar.

À minha família e ao seu apoio incondicional durante todo o meu percurso de vida, sem o qual não seria possível concretizar os meus objetivos.

À pessoa que me conhece como ninguém, que cuida e estima com uma incondicionalidade que desconhecia. Pela companhia, pelo afeto e pela constante presença, até na própria ausência, eu estou eternamente grato.

Por fim, mas não menos importante, agradeço à minha segunda família que criei em Aveiro, amigos de laços inquebráveis, com os quais passei a melhor fase da minha vida. Com eles ri, chorei, aprendi e desaprendi um pouco por vezes. Aquilo que sou hoje tem um pedaço de cada momento que passei com eles. Aveiro nunca seria o mesmo sem essa família. Guardo-vos a todos na memória. Convosco Aveiro é para sempre, Aveiro é a nossa casa.

Aveiro é nosso.

palavras-chave Mestrado; biomedicina farmacêutica; estágio curricular; investigação clínica; ensaios clínicos; coordenador de estudos; farmacovigilância; gestão de dados.

resumo

O presente relatório descreve em detalhe as tarefas e atividades desenvolvidas no contexto de um estágio curricular durante o segundo ano do Mestrado em Biomedicina Farmacêutica, da Universidade de Aveiro. Este estágio teve lugar na Unidade de Farmacologia Clínica do Professor Joaquim Ferreira, do Instituto de Medicina Molecular, de 14 de setembro de 2015 a 27 de junho de 2016.

Esta experiência permitiu-me pôr em prática aquilo que aprendi no mestrado durante dez meses. Tive a oportunidade de trabalhar em três áreas diferentes da biomedicina farmacêutica: farmacovigilância, coordenação de ensaios clínicos e gestão de dados.

Durante o estágio, surgiram múltiplas dificuldades e obstáculos. Contudo, consegui ultrapassá-los, melhorando as minhas capacidades profissionais, tais como organização, responsabilidade, comunicação, espírito critico, entre outras qualidades fundamentais para ser um bom profissional.

Em conclusão, este estágio curricular permitiu o meu crescimento, não só como profissional, mas também como pessoa. Considero que tenha sido um desafio concretizado com sucesso e estou consciente que me abriu muitas janelas para a minha carreira futura.

keywords

Master's degree; pharmaceutical medicine; curricular internship, clinical reasearch; clinical trials, study coordinator, pharmacovigilance; data management.

abstract

This report describes in detail the tasks and activities developed in the context of a curricular internship during the second year of the Master's degree in Pharmaceutical Medicine of the University of Aveiro. This internship took place in the Professor Joaquim Ferreira's Clinical Pharmacology Unit (CPU) of the *Instituto de Medicina Molecular,* from September 14th, 2015 to June 27, 2016.

This experience allowed me to put in practice what I learned from my master's degree during ten months. I had the opportunity to work in three different areas of pharmaceutical medicine: pharmacovigilance, clinical trial coordination and data management.

During the internship, several difficulties and obstacles showed up. However, I managed to surpass them, improving my professional skills, such as organization, responsibility, communication, critical thinking, among other fundamental qualities to be a good professional.

In conclusion, this curricular internship allowed me to grow up, not only as a professional but also as a person. I think it was a successful challenge and I'm aware that it has opened many windows to future career.

Table of Contents

List of Figures

List of Abbreviations

AD	Alzheimer's Disease
ADME	Absorption, Distribution, Metabolization and Excretion.
ADR	Adverse Drug Reaction
CAML	Lisbon Academic Medical Centre *(Centro Académico de Medicina de Lisboa)*
CIC	Clinical Investigation Centre *(Centro de Investigação Clínica)*
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CRO	Contract Research Organization
CT	Clinical Trial(s)
CTA	Clinical Research Associate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAP	Familial Amyloid Polyneuropathy
FMUL	School of Medicine of University of Lisbon *(Faculdade de Medicina da Universidade de Lisboa)*
GVP	Good Pharmacovigilance Practice
HD	Huntington's Disease
HSM-CHLN	Santa Maria Hospital *(Hospital Santa Maria – Centro Hospitalar Lisboa Norte)*
IME	Important Medical Events
IMM	Instituto de Medicina Molecular
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde I.P.
MA	Marketing Authorization
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
NFC	Central Pharmacovigilance Nucleus *(Núcleo de Farmacovigilância do Centro)*
OS	Observational Study(ies)
PD	Parkinson's Disease
SAD	Single Ascending Dose
SAE	Serious Adverse Event

SC	Study Coordinator
SNF	National System of Pharmacovigilance *(Sistema Nacional de Farmacovigilânica)*
SOP	Standard Operation Procedure
UFLVT	Lisbon and Vale do Tejo Pharmacovigilance Unit *(Unidade de Farmacovigilância de Lisboa e Vale do Tejo)*
UFN	North Pharmacovigilance Unit *(Unidade de Farmacovigilância do Norte)*
UFS	South Pharmacovigilance Unit *(Unidade de Farmacovigilância do Sul)*
URF	Regional Pharmacovigilance Unit *(Unidade Regional de Farmacovigilância)*
WHO	World Health Organization

1. Introduction

This document is the final report of my curricular internship performed during the second year of the Master's degree in Pharmaceutical Medicine of the University of Aveiro. It lasted 10 months, from September 14th, 2015 to June 27, 2016. The host institution was the Clinical Pharmacology Unit (CPU) of the *Instituto de Medicina Molecular* (IMM).

The internship was divided in 3 subunits: 2 months in pharmacovigilance practice; 5 months in clinical trials coordination and 3 months in data management. The aim was to learn and get experience in different areas instead of only one. It was an extended training of the real-world environment and a preparation to initiate my professional career.

Before the beginning of the internship, I established some goals that I wanted to achieve. Maximum effort and spirit of sacrifice would be essential to accomplish them, in order to be better as a person and professional. Once I already had an idea of the subunits I would be working on, I committed to myself to accomplish the following objectives:

- Develop my research and data management skills;
- Improve my scientific writing skill;
- Acquire qualification to be study coordinator and improve communication with patients;
- Acquire qualification to work in pharmacovigilance and to get a better know-how of the national adverse drug reaction notification system.
- Improve my teamwork skill.
- Acquire sufficient work versatility, to be prepared to try new professional experiences and challenges.

This report is divided in 6 chapters. Apart from this first introductory chapter, the second one is an overview of the host institution, where I describe the structure of IMM and the main functions of the subunits of CPU.

The third chapter is a set of the current knowledge about my main area of study – Clinical research and pharmaceutical development. Majorly based on bibliographical references, it is the background of the 3 subunits of my internship.

The fourth chapter is where I describe the developed activities at each subunit.

The skills learned, the difficulties experienced, the milestones overpassed and other relevant events are discussed in the fifth chapter. The conclusions of that discussion are presented in the last chapter.

2. Host Institution Overview

2.1. Instituto de Medicina Molecular

Instituto de Medicina Molecular (IMM) is a portuguese scientific institution focused on basic, clinical and translational biomedical research, in order to contribute to a better understanding of human diseases. Founded in December 2001, IMM is a private, non-profit association and currently hosts approximately 400 researchers (1) and supports with scientific postgraduate training of young graduates, physicians and other health-care professionals.

IMM has been improving its scientific productivity since its creation, reaching over 4500 citations from publications of IMM researchers in 2013, who have published, in the same year, 89 papers (out of 305) in peer reviewed journals of impact higher than 5, and 23 in journals of impact higher than 10 (2).

Several IMM teams were recognized with national and international awards, including the Micahel J. Fox Innovation award, the *Prémio Nacional de Inovação BES*, the *Pessoa* award, the *Crioestamina*l award, amongst many others (2).

IMM, Faculty of Medicine of Lisbon (FMUL) and Santa Maria University Hospital (HSM-CHLN) recently formed the Lisbon Academic Medical Centre – (CAML), a consortium aiming to promote the academic dimension in clinical practice, improve research development and innovation of medical education and health sciences. CAML renews the concept of an university hospital, ensuring the necessary compatibility of medical education with research and development of the health care mission (3). It has triggered the creation of start-up companies and several research collaborations on diverse areas of biomedical technologies, by facilitating the translation of research into clinical practice.

The organisation of IMM is represented in figure 1. The blue shaded boxes represent the research unit where I did my curricular internship.

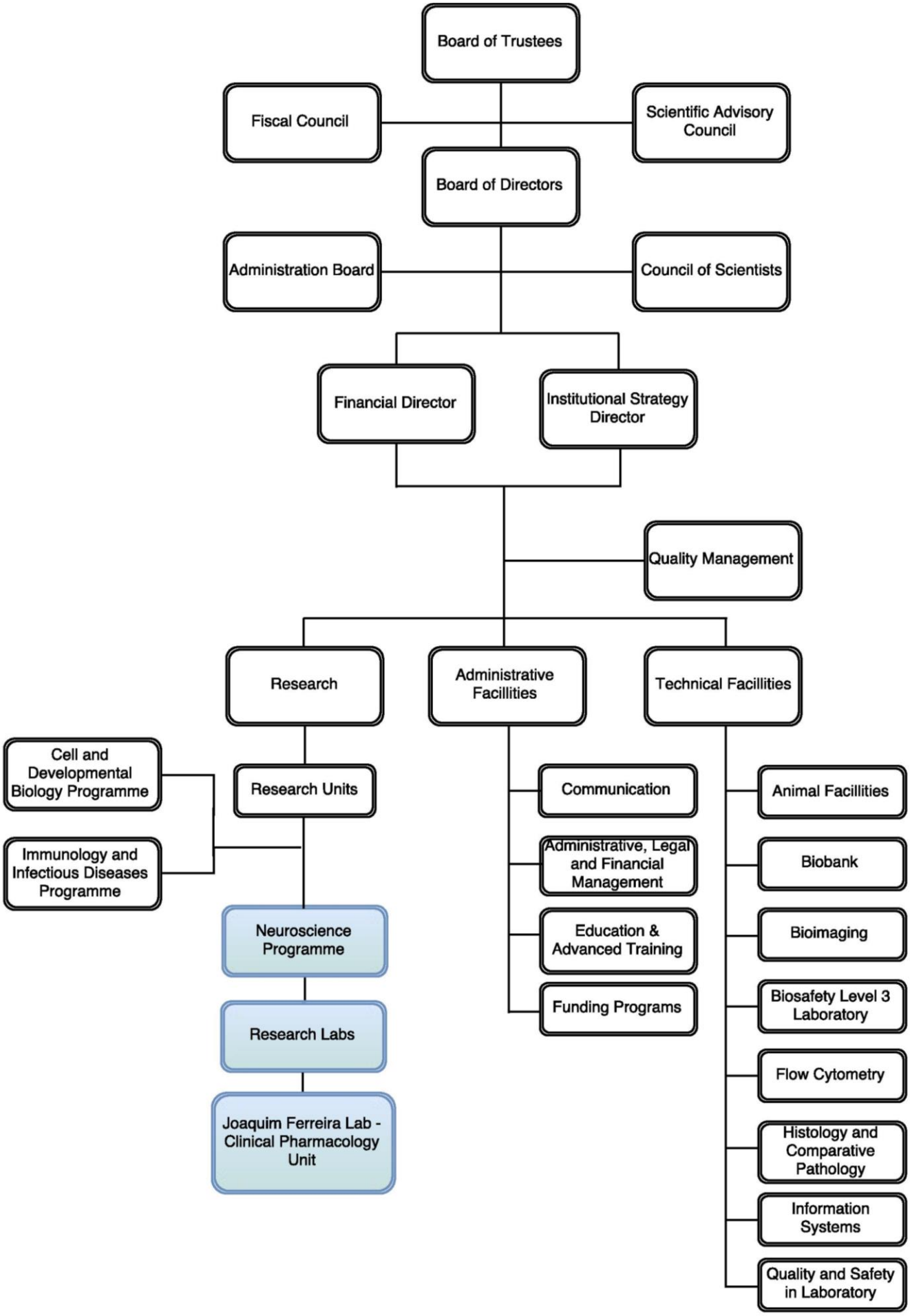

Figure 1 - Structure and Organization of *Instituto de Medicina Molecular* (Adapted from: IMM *Lisboa – Organização* (1), available at https://goo.gl/d2bbuB).

Clinical Pharmacology Unit

The CPU was created on 1st of July of 2013 and it is currently directed by Joaquim Ferreira, MD/PhD, clinical specialist and associate professor at School of Medicine of Lisbon. CPU has the mission to contribute to the development of effective and safe therapeutic interventions in neurological diseases, establishing optimized methodologies for the design, conduction, analysis and report of clinical trials (CT) (4). This unit also envision collaborations with pharmaceutical industries, leading to a better conduction of CTs, assuming a shared role in the early stages of clinical development (4).

The activities of CPU are divided in sub-units, as shown in figure 2, and each one of them will be described in the next paragraphs.

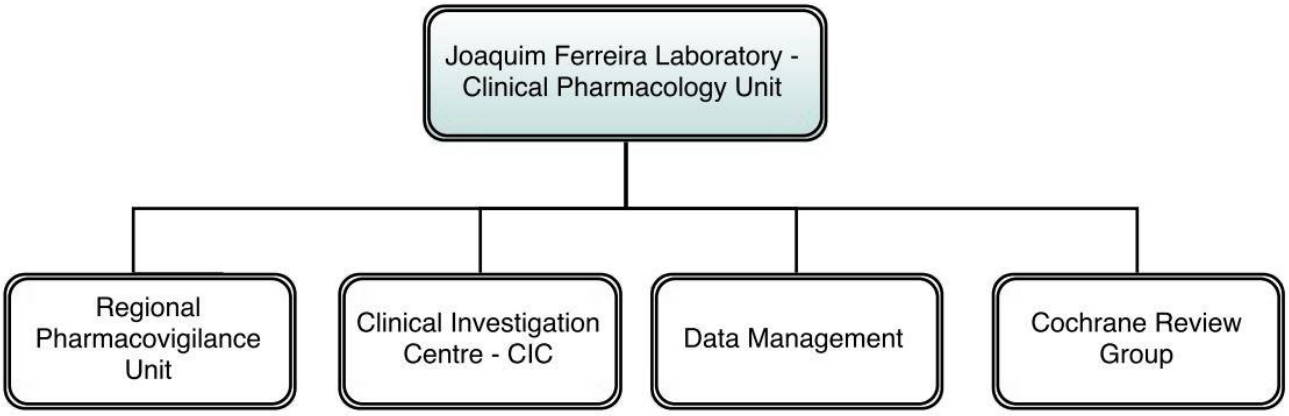

Figure 2 - Sub-units of the Clinical Pharmacology Unit – IMM

2.2.1. Regional Pharmacovigilance Unit

CPU hosts a regional unit of the National Pharmacovigilance System (SNF) - *Unidade de Farmacovigilância de Lisboa e Vale do Tejo* (UFLVT).

The National Pharmacovigilance System was created in 1992, to ensure the safety of commercialised medicines through the promotion and dissemination of safety control methods, especially in relation to spontaneous reports of Adverse Drug Reactions (ADRs). In the year 2000, the SNF was decentralized in Regional Pharmacovigilance Units (URFs): North, Central, South, and Azores (5). Over the years, more Portuguese people have learned about the Pharmacovigilance System and its concept, so the numbers of spontaneous notifications (SN) of ADRs have been increasing. These high

numbers of notifications lead to a restructuring of the URFs in 2013, and the former South Pharmacovigilance Unit became the current UFLVT, and a new South region unit was created with functions linked to the South Regional Health Administration (5). The INFARMED I.P, the Portuguese National Authority of Drugs and Health Products, hosts the SNP and became responsible for the reception of notifications from Madeira and Azores islands. Therefore, there are currently four URFs linked to University structures (5):

- North Pharmacovigilance Unit (UFN) – School of Medicine of University of Porto.
- Central region Pharmacovigilance Nucleus (NFC) – University of Coimbra.
- Lisbon and Vale do Tejo Pharmacovigilance Unit (UFLVT) – School of Medicine of Lisbon.
- South Pharmacovigilance Unit (UFS) – School of Pharmacy of University of Lisbon.

Each URF has the function to receive, classify, process and validate spontaneous notifications with a minimum expected rate of 150 SN / million inhabitants / 1 year. UFLVT covers an area of about 3,6 million inhabitants. Other functions of the URFs are the communication to the Pharmacovigilance Department of INFARMED of SN and the promotion and dissemination of SNF and SN in the respective geographical areas (5).

Further on this report I will describe my activities at UFLVT.

2.2.2. Clinical Investigation Centre

The Clinical Investigation Centre (CIC) is the CPU sub-unit responsible for CTs and Observational Studies (OS) conduction and coordination. It is physically located on the 6th floor of the Neurology Department of HSM-CHLN and holds a team of professionals, including neurologists, nurses, laboratory technicians, hospital pharmaceuticals and study coordinators, all contributing for a good and correct trial conduction.

Neurological Diseases are the main focus of CIC. There are several ongoing CT for Movement Disorders and Dementia, such as Parkinson's Disease (PD), Familial Amyloid Polyneuropathy (FAP), Huntington's Disease (HD), Alzheimer's Disease (AD), Multiple Sclerosis (MS), epilepsy and psychosis. It is an active centre in terms of patient recruiting and care, always looking forward to new CT and/or OS.

CIC is the central point of communication between sponsors and health care professionals. Also, it is responsible for involving several departments of the hospital in the clinical studies, for better evaluation of patient tests and exams. For instance, some

professionals from the Cardiology department are involved in several CTs, being responsible for ECG trace evaluation, performing echocardiograms and other issues related to cardiovascular safety assessments.

The hospital pharmacy has a clinical trial unit as well. It is responsible for receiving, preparing, manage and storage the study drugs and related materials. Therefore, the communication between the hospital pharmacy and CIC is constant and almost daily. They provide the study medication prescribed by CIC on study patient visits. All the study medication that patients bring to CIC return to the hospital pharmacy, either it is used, damaged, out of date or simply not taken.

Working directly with CIC, there are study nurses responsible for drug infusions and blood samples collection, and a lab technician to process those samples.

CIC also counts with clinical psychologists or “raters”, who evaluate patients with the gold-standard scales for neurological assessments, for example, C-SSRS (Columbia Suicide Severity Rating Scale), ADAS-cog (Alzheimer’s Disease Assessment Scale Cognitive Behaviour Section), HD-CAB (Huntington's Disease Cognitive Assessment Battery), among others. These rating scales are increasingly used as primary or secondary outcome measures in clinical studies in neurology (6). They are an important key upon which decisions are made that influence patient care and the adequacy of those decisions depends directly on their scientific quality (7).

At last, but not the least, the Study Coordinators (SC) are the main role in CT management and all of the procedures involved. They have good understanding of the CT protocols, preparing each patient visit and communicating with all the personnel involved, to make sure that everything is done per protocol. Data collection is one of their main functions. There can be blinded and unblinded SC for the same studies, so unblinded SC work with more sensitive data, which blinded personnel cannot see. Study coordination was my role in CIC, during my internship. I will describe the activities I performed as a SC further in this document.

2.2.3. Data Management

This subunit is responsible for data treatment, biostatistics and medical writing. It focuses on data gathering and management of the lab’s several projects and studies. It has qualified employees that work with different types of databases (SQL, R, etc.) and do the statistical analysis. This work will result in interim analysis, to rectify the quality, safety

and integrity of the studies, and final reports and other important papers to be published in a later stage.

Here I had the opportunity to perform database construction and a statistical analysis. I will describe them with more detail later on this report.

2.2.4. Cochrane Review Group

The Clinical Pharmacology Unit employs a representative of the Portuguese Branch of the Iberoamerican Cochrane Centre. The Cochrane Review Group consists in a global independent network of researchers, professional, patients, carers, and people interested in health. Around 130 countries work together, with contributions in the fields of medicine, health policy, research methodology, and consumer advocacy, to promote the development of systematic reviews and meta-analysis.

Although I did some work related to systematic reviews, I had no direct contact with this subunit or developed activities for it.

3. State of the Art

This chapter intends to contextualize my internship and the areas of pharmaceutical medicine I worked on, with the current state of clinical research and development. Also, it highlights the important aspects of drug development, since its discovery until it reaches market, the importance of data management during the clinical trial phase and the continuous safety evaluation, by pharmacovigilance.

3.1. Clinical Research and Drug Development

Clinical research is a subdivision of medical science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment regimens for humans (8). Putting it simple, it involves human participants and helps translate basic research into new treatments and information to benefit patients (9).

Different types of clinical research are used depending on what the researchers are studying (10). Prevention research aims to find better ways to prevent disorders from developing or returning. Types of prevention may vary, including new vaccines, or simply lifestyle changes. There is also diagnostic and screening research which looks for better ways to identify specific disorders and detect them in humans. Treatment research usually involves an intervention such as medication, psychotherapy, new medical devices, or new approaches to surgery. There are more types of clinical research, such as quality of life assessments, genetic studies and epidemiological studies that also contribute to a better clinical practice.

Besides all these types of clinical research, usually they are all put together in two different groups: observational studies and interventional studies. Observational studies, also called epidemiological studies, are those where the investigator is not acting upon study participants, but instead observing natural relationships between factors and outcomes (11). Interventional study designs, also called experimental study designs, are those where the researcher intervenes at some point throughout the study (11).

Clinical trials are interventional research studies that test how well new medical approaches, like new drugs, work in people. But for a new drug get to this point, it is necessary to go through a complex process of preclinical development first, right after its discovery. The rapid growth in scientific advances is enabling a greater understanding of diseases, but companies often focus their research and development where the science is

difficult and the failure risks are higher (12). On average, it takes between 10-12 years for a new medicine to go to the marketplace, since its discovery. CTs take, usually, 6 of those years to perform. The average cost to research and develop each successful drug is estimated to be €1.3 billion (figure 3). This value includes the cost of failures. The overall probability of clinical success, i. e., the likelihood that a drug entering clinical testing will eventually be approved is estimated to be less than 12% (12).

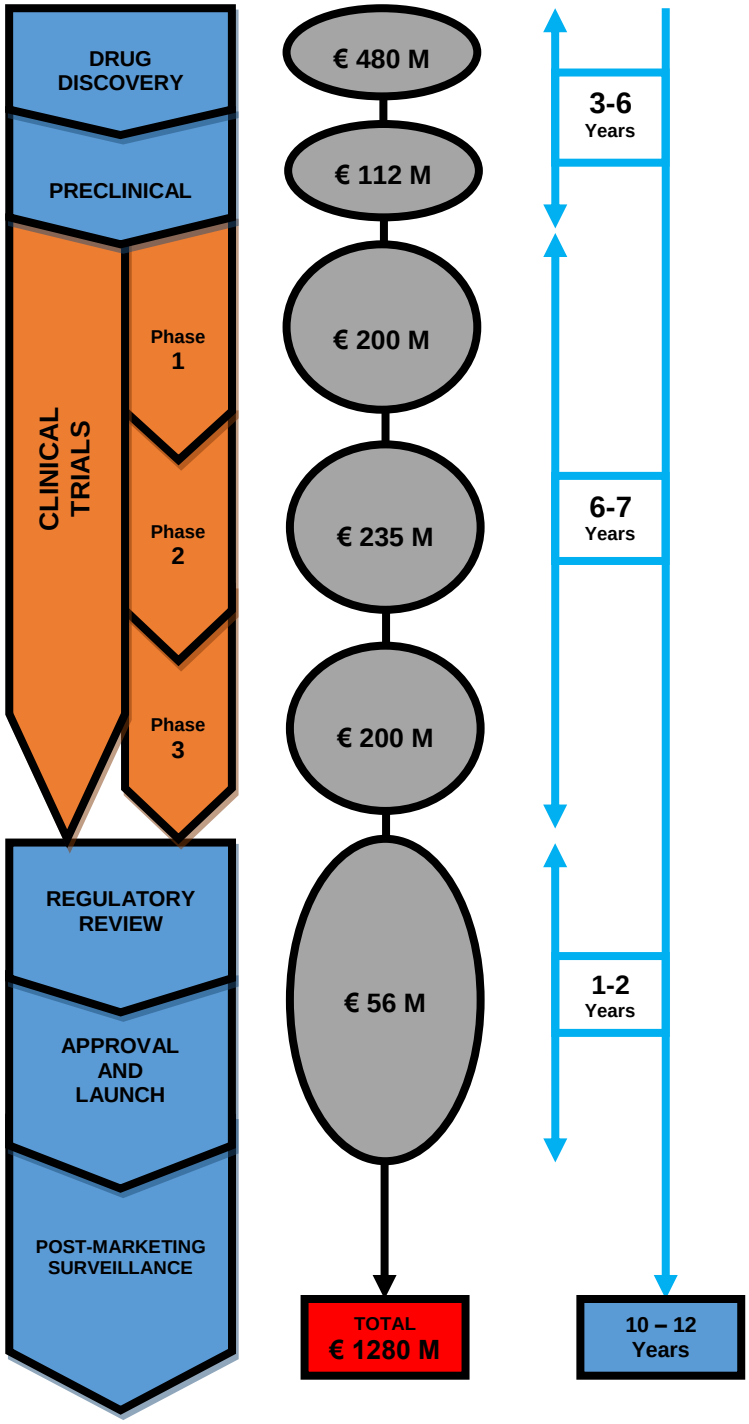

Figure 3 – Cost and Time of developing a new medicine. (Adapted from Cancer Research UK – "Dance with pharma" (33)**, available at: http://bit.ly/cruk-pharma ; and from GSK – "How we discover new medicines"** (13)**, available at: http://bit.ly/2ep7Kbi**

3.2. Drug Discovery and Preclinical Research

The discovery process includes the early phases of research, which are designed to identify an investigational drug and perform initial tests. On this phase, researchers hope to identify a promising drug for further studies in laboratories and in animal models (12). Normally, researchers discover new drugs through new insights into a disease process, through tests of molecular compounds to find possible beneficial effects against any of a large number of diseases, through existing medicines on the market, but for a new therapeutic indication, or trough new technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material (13).

During this phase, thousands of compounds can be used, but only few will continue to further tests. Researchers will continue this process until they find a promising drug for development (13). Once it happens, researchers develop more experiments in order to gather information about its absorption, distribution, metabolization and excretion (ADME) properties, mechanisms of action, potential benefits, dosages and routes of administration, side effects, among other characteristics of the compound (13).

With one or more compounds identified, researchers turn their attention to extensive testing in a preclinical phase. In this phase of research, scientists carry out both *in vitro* and *in vivo* tests, to determine if the lead compound is ready to be tested in humans. *In vitro* (“glass” in Latin) tests are experiments conducted in the laboratory, while *in vivo* (“life” in Latin) studies are those conducted in living cell and tissue cultures and animal models.

Through this, researchers try to understand how the drug works and what potential side effects on humans might have (12), with detailed information on dosing and toxicity levels. Usually, it is not worth to perform extensive testing on the promising drug, because it might be spent too much money to get data that is not needed. What is really necessary is to guarantee whether the drug is safe and ready for human trials.

3.3. Clinical Trials

Clinical trials are research studies that test how well new medical approaches work in people (14). They look at new ways to prevent, detect, or treat disease. Treatments might consist in new drugs or combinations of drugs, new surgical procedures, devices, or new ways to use existing treatments (15).

CTs follow a specific study plan – the protocol. This document is developed by the researcher or manufacturer and is carefully designed to safeguard the participants' health and answer specific research questions, such as (15) (16):

- Who qualifies to participate (selection criteria);
- How many people will be part of the study;
- How long the study will last;
- Whether there will be a control group and other ways to limit research bias;
- How the drug will be given to patients and at what dosage;
- What assessments will be conducted, when, and what data will be collected;
- How the data will be reviewed and analysed;

CTs are funded by various organizations or individuals, including physicians, foundations, medical institutions, voluntary groups, and pharmaceutical companies. These are called the sponsors (15). The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operation procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, good clinical practice (GCP), and the applicable regulatory requirements (17).

Before the decision of participating in the study, participants must be given an informed consent – a document that provides the key facts about a clinical trial, such as its purpose, duration, required procedures, and who to contact for further information. The informed consent document also explains risks and potential benefits. The participant then decides whether to sign the document (15). The process of informed consent continues throughout the study. To help someone decide whether or not to participate, members of the research team explain the details of the study. Informed consent is not a contract. Volunteers are free to withdraw from the study completely or to refuse particular treatments or tests at any time (15).

CT's follow a typical series from early, small-scale, phase 1 studies to late-stage, large scale, phase 3 studies (16).

3.3.1. Phase I

In Phase I trials the candidate drug is tested in people for the first time. These studies are usually conducted with a small number of healthy volunteers, generally 100 or less. The main goal of a Phase I trial is to assess the safety of the medicine when used in

humans. Researchers look at the drug's pharmacokinetics (what the organism does to the drug), and pharmacodynamics (what the drug does to the organism) (12).

The typical phase I trial has a single ascending dose (SAD) design, meaning that subjects are dosed in small groups called cohorts. Each member of a cohort might receive a single dose of the study drug or a placebo. A very low dose is used for the first cohort. The dose is then escalated in the next cohort if it is safe to do so. Dose escalation is stopped when maximum tolerability and/or maximum exposure is reached (18).

This phase lasts several months and only approximately 70% of drugs move to the next phase (16).

3.3.2. Phase II

Phase II trials are performed on larger groups (100 to 500 patient volunteers (12)) of patients and are designed to assess the efficacy of the drug and to continue the phase I safety assessments. Most importantly, phase II clinical studies help to establish therapeutic doses for the large-scale phase III studies (18). Phase II studies design depends on the compound's mechanism of action. Many patients receiving the drug are compared with patients receiving a different treatment, either placebo, or a different drug that is usually considered the standard of care for the disease (12). The length of this phase can be from several months to 2 years, and approximately 33% of drugs move to the next phase (16).

3.3.3. Phase III

Phase III trials generate statistically significant data about the safety, efficacy and the benefit-risk relationship of the investigational drug. Phase III trials may enrol 1,000 to 5,000 patients across several clinical trial sites all over the world. This phase of research is essential to determine if the drug is safe and effective (18). These trials are the most expensive, time-consuming and difficult to design and run. Therefore, drugs that do not show promising results in phase II do not continue to phase III (12). Normally, a contract research organization (CRO) is contracted by the sponsor to manage and lead the company's trials, duties and functions (19).

Phase III trials have an average duration between 1 to 4 years and only 25-30% of the drugs successfully end this phase with positive results and get authorized in market (16).

There is also a Phase IV, which consists in post-marketing trials involving safety surveillance (pharmacovigilance) and ongoing technical support after approval. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive purposes or other reasons (18).

3.3.4. Clinical data management

Clinical data management is a critical phase in clinical research, which leads to generation of high-quality, reliable, and statistically sound data from clinical trials. The quality of this data has an important role in the study's outcome. It consists in the process of collection and management of subject data in compliance with regulatory standards (20), including the Regulation (EC) No 45/2001, which seeks to protect the liberties and fundamental rights of individuals with respect to the processing of the personal data (21).

Clinical data management includes several procedures such as: Case Report Form (CRF) designing, CRF annotation, database designing, data-entry, data validation, medical coding, data extraction, and database locking (20).

Novel technology advances have allowed the developing of new and sophisticated tools, enabling clinical data management to handle large trials and ensure the data quality even in complex trials. This also helps to reduce drastically the time it takes from drug development to marketing (20).

3.4. Pharmacovigilance and Drug Safety

Once placed on the market, all medicinal products in the EU are subject to a strict testing and assessment of their quality, efficacy and safety before being authorised. They continue to be monitored so to assure that any aspect which could impact the safety profile of a medicine is detected and assessed and that necessary measures are taken. This monitoring is called pharmacovigilance (22).

Pharmacovigilance has been defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (23). The main objectives of pharmacovigilance include prevention of harm from adverse reactions in humans and promotion of the safe and effective use of medicinal products (23).

The initial idea and concept of pharmacovigilance came with the WHO Programme for International Drug Monitoring in 1968, in response to the thalidomide disaster in the 1960s, where about 10,000 babies were born with deformities as a result of the adverse effects of thalidomide (24).

The current need of pharmacovigilance is due to the limited amount of information available from CTs. Patients in CTs are selected carefully and followed up very closely under controlled conditions. However, after marketing authorization (MA), patients using a medicine may have other diseases and may be taking other medicines. It will also be used in a larger number of patients, increasing the possibility of rare side effects being discovered. Some side effects may only start to emerge once a medicine has been used for a long time (25).

The good pharmacovigilance practice (GVP) provides guidance on the conduct of pharmacovigilance for specific product types or specific populations in which medicines are used (23). These practices are designed to efficiently and effectively detect and alert the drug safety professional to new and potentially important information on drug-associated adverse reactions (26). GVP apply to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States (25).

.

4. On-the-Job Training

4.1. Activities Developed in Pharmacovigilance

The assessment of quality, efficacy and safety of medicines does not end after MA. Any aspect which could impact their safety profile is detected and assessed by continued monitoring through pharmacovigilance (22).

Before MA, clinical trials, if performed strictly and correctly, provide sufficient information about safety and efficacy of the drug for its approval. However, in most of the cases, the target population is far greater than the tested sample. So, the real-world safety and efficacy must be continuing monitored because there could be several drug effects yet to be discovered and assessed. Not only adverse events, but also harmless secondary effects or even new therapeutic indications.

As I mentioned before on this report, the UFLVT function is to receive, classify, process and validate spontaneous notifications of ADRs. On my first week, I read about ADRs and the pharmacovigilance unit. The Management Quality Plan was essential to understand the dynamics and procedures in a systemized way. Also, I read European guidelines, including the EMA guideline on GVP. The GVP guideline is divided in several modules and aims to facilitate the performance of pharmacovigilance in the European Union, covering medicines authorised centrally via the Agency as well as medicines authorised at national level (27).

On the weeks after that, I was assigned to validate spontaneous notifications of ADRs that are sent to UFLVT via e-mail, letter, phone or fax. A validated notification has the minimum information required to be processed (28):

- Adverse reaction description;
- Identification of the medicine suspected to have caused the adverse reaction;
- Information of the person who experienced the adverse reaction;
- Contact details of the reporter of the adverse reaction.

When some of these were missing, the reporter would be contacted in order to provide core information and other details about the case.

During validation, it is crucial to identify whether the reported ADR is a Serious Adverse Event (SAE). An adverse event is any undesirable experience associated with the use of a medical product in a patient (29). The event is serious when occurs one of the following outcomes: death; life-threatening; hospitalization (initial or prolonged); disabilities

or permanent damage; congenital anomaly/birth defect; required intervention to prevent permanent damage; or other serious important medical events (IME) (29). A list of IMEs released by EMA is available for consulting. The responsible physician can consider whether it is a SAE, after appropriate medical judgement, even if it does not fit in any of the outcome stated above. If the reported patient experienced a SAE, then it must be reported to INFARMED within 24 hours.

After validation, I inserted the notification's information on INFARMED's online tool for ADRs reporting: Portal RAM. While I was doing this, one of the obstacles was the translation of the ADR description, sometimes written in popular language, to a scientific and standardized designation. MedDRA dictionary was the ideal tool for this task, since the online portal accepted ADR inputs in MedDRA language only. MedDRA stands for "Medical Dictionary for Regulatory Activities" which is a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans (30). It was developed under the auspices of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (30). When all information was successfully submitted to Portal RAM, the notification would be in standby until the reporter was contacted for further information and to know the current state of the ADR (persisting, improving, or cured). This is preferably done by phone call in a maximum of 7 days after the reception of the notification.

Another of my activities was to elaborate narratives of the notifications, i. e., to write a text with all the relevant information of the case, starting with the identification of the patient, the SAE(s) experienced, the suspected medicine (start and finish dates; dosage), concomitant medication, medical history, etc. This is one of the final fields to fill in the Portal RAM.

In the end, all notifications are sent to the physician responsible for the causality attribution. He, after medical judgment, will attribute the relation between the suspected medicine and the ADR as unlikely, possible, probable, certain, not related or not assessable. Then a causality report is generated and sent to INFARMED and to the reporter.

Until the case is considered closed, UFLVT will stay in contact with the reporter to keep him updated with the decisions made about the case and to assess the evolution of the ADR.

During the time I was in UFLVT I have learned quite much about pharmacovigilance practice. I even had the opportunity to participate in a 4-day intensive course of

Pharmacovigilance, developed by UFLTV personnel. At the end of the internship, I considered myself capable of doing some of the activities autonomously.

4.2. Training in Coordination of Clinical Trials

When I began the internship in coordination of clinical trials, the studies were divided and assigned to me and to my colleagues. My main function as a SC was to coordinate the few studies assigned to me. My colleagues' studies were not my responsibility. Although, when help was needed and, effectively, it could be given without neglect other studies, it would be valued.

CIC, that hosted me during five months, works only with neurology studies. The CTs that I helped to coordinate allowed me to have contact with three neurological diseases: Parkinson disease (PD), Huntington disease (HD) and familial amyloid polyneuropathy (FAP).

First, I had to read the protocols of all my studies to understand their nature, their methods, the documentation, materials and everything that was indispensable to prepare the visits of the participants to the centre, and the whole scheduling of the study. Most of the times, there was a pocket protocol provided by the sponsor, for consulting anywhere and anytime to answer some last minute questions.

One of the most important tasks was to prepare study visits. In every study protocol, there was a systemized schedule of all the participant's visits. There, it was possible to retrieve all the information needed for that visit: which variables would be measured to the patient, questionnaires, analysis and exams, what would be analysed in the blood samples and how to process them and get them ready to send to the central laboratory. Therefore, in the days before the visit day, I would check all this information and prepare the visit. I gathered all documentation needed (visit checklists, questionnaires, etc.) from the source files, and the blood/urine sample collection kit(s) necessary for that visit. Usually, these kits were identified and organized by visit. They contained, mostly, collection tubes, for blood collection by a phlebotomist, and the transfer tubes, the ones to be sent to the central with the blood serum, obtained by centrifugation. In some studies, collection and transfer tubes came already labelled, while in others I had to do that manually with the labels provided separately.

In addition, every personnel involved in that visit would be contacted and informed of their tasks for that day. Patients would be contacted as well, in order to remind the hour

and date of the visit and of special care needed or medication, documents, etc. that they had to bring with them to the centre.

When a visit included treatment with the test drug, it had to be requested to the hospital's pharmacy, to pharmacists adequately trained for that CT, by Interactive Voice Response System (IVRS) or by Interactive Web Response System (IWRS). The first consists in a phone call to an automated system where, with the patient ID, visit number, a secret password and other relevant information (depending on the study), it was possible to prescribe medication to that patient. The second one is by a website, essentially with the same methods.

Thereby, with all the elements needed and all people informed, the visit would occur more fluidly, with less time waste. The efficiency of a visit was directly dependent of its good preparation.

On days with patients' visits, mostly my function was to accompany them to the right places, fill the checklists with the information as soon as I got it, such as weight, blood pressure, temperature, etc. and the time they were measured, and to process the blood and urine samples. Every study had a laboratory guide with instructions for all samples on how to process them: clotting time after collection, speed and temperature of the centrifuge, quantity needed for the transfer tubes, shipping method (ambient or dry ice) and storage conditions.

Besides patient visits, I had another important function in back office: CRFs data input and query resolution. A CRF is a specialized document in clinical research, designed to collect the patient data in a clinical trial (31). Although paper CRFs are still used largely around the globe, most of the centre's studies used electronic case report forms (eCRFs). They are properly designed to receive all necessary data demanded by protocol. It is a dynamic file that requires constant updates and monitoring. The eCRFs have the advantage of being programmed to be sensitive about the information inserted in the system. Despite the personnel responsible for monitoring these CRFs, the system itself generates automatic queries if data is not inserted by the predetermined standards. When these and other queries showed up in the eCRF, I had to solve them, by correcting transcription errors, consulting source files, etc. depending on the nature of the query.

All CTs had scheduled monitoring visits by the clinical research associate (CTA). Before that day, I prepared and organized every documentation, patient files and other relevant details to facilitate the monitoring process. In that day, the CTA was responsible to ensure the high quality of data and to check if there were any protocol deviations and mark them for resolution. Also, it was a good time for answering any questions about the

study, to discuss the best way to perform some tasks and to give an overview about the current situation of the study.

These were my activities developed at the CIC, from which I learned much. Also, I developed skills that I think to be essential for every professional, especially in healthcare and clinical investigation areas.

4.3. Activities Developed in Data Management

The last stage of my internship was a data management experience. Actually, my activities here were not as many as I initially expected, but it doesn't mean that I didn't learn with it.

My major activity was to organize a database and fill any missing information. This was a database of four clinical studies, each one with few hundreds of patients (between 100 and 300). My job was to check the common variables among all studies and to retrieve that information from raw data to an organized excel file. It took some time to complete this task, because of the standardization of every variable. For example: transform variables with "*sim / não";* "y / n"; etc. into a standard format, like "Yes / No"; or make the conversion of values of the same variable to the same unit of measurement.

The aim of this database was a complete statistical analysis of all studies. This evaluation used advanced statistical methods that I never used and wasn't comfortable with. Thereby, my task was only to finalize the database. The statistical evaluation would be performed by my superior in data management.

Nevertheless, the other task assigned to me was a descriptive statistical analysis. This one wasn't so time consuming. It consisted in calculate means, medians, confidence intervals at 95% (CI=95%), minimums and maximums of several variables, such as weight, age, and the other study specific measures at three different stages of the treatment. To do this, I used the SPSS tool to analyse the database given to me. I performed the data selection and then, with knowledge acquired from the master's statistics module, worked with SPSS to make a descriptive statistical analysis. After obtaining the results, I created a slideshow so I could display those results in an organized and easy way to understand.

This last task was part of an interim analysis of a study. An interim analysis is an evaluation of the current data from an ongoing trial, in which the primary research question is addressed, and which has the potential for modifying the conduct of the study (32). With this activity, I was able to take the first steps of an interim analysis.

Although I performed only few activities at data management internship, they were very valuable and instructive tasks.

5. Discussion

This chapter is an overview of the impact that this internship had in my life, at all levels. I intend to demonstrate what I knew at the start of it and how I grew up and learned, to be the person with much more knowledge that I am today. In other words, this chapter highlights the reason of this internship and the importance of it.

The internship at the CPU was indeed a changing experience. The idea of a first real-world work experience can be frightening at the beginning, but it is rewarding at the end. Ten months of activities developed with a multifaceted team did make a difference in my evolving process, not only as a person but as a professional too. The environment was ideal to learn and improve work skills, but difficulties and obstacles appeared when least expected and things tended to get complicated sometimes. For me, the real challenge of this internship was to surpass those obstacles and solve imminent problems that are not in the books.

At the pharmacovigilance unit, the challenge was the unexpected number of notifications that we could receive in only one day. Each notification requires a whole process, as I described early on this report. The dynamic of the unit is consistently fluid and well structured, so, usually, the notification processing occurs normally without any delays. Although, in some days, the quantity of notifications sent to the unit is higher than normal, increasing workload significantly. The challenge here was to do the same things I've progressively learned to do, but with the pressure of doing it faster with the same quality of work. On the first times, I had some difficulties to conciliate everything, including the pressure, but in the end, I had my performance improved with very few difficulties.

In my opinion, increase of workload happens in every work environment, so I was satisfied with my evolution and quick adaptation to this first obstacle. This skill was very important since, after the pharmacology unit, I went to CIC, to coordinate CTs, where the workload is much more unstable.

The things I've learned from the pharmacovigilance internship were very interesting and quite surprising. There, I had the opportunity to integrate in a real system of constant evaluation and control of medicines. I was encouraged to read and to learn in every step of my training. I would like to participate in an auditing preparation process but I didn't have the opportunity to do so, because I started the internship few weeks after an auditing by INFARMED. It was an exceptional experience and the welcome was very pleasant. In the end, I was treated like another professional and it really felt that I was part of this team.

The training at CIC was quite more challenging. Half of my curricular internship (five months) was spent as SC, so there was enough time to encounter all types of obstacles. Most of the activities developed in this centre are dependant of more than one person, so it was easy for something to go wrong. This was my first milestone here: to take fully control of my tasks in order to guarantee that everyone is informed and the right information is given, so that misunderstandings could be avoided. It seems easy, but when many tasks are pending, it's difficult keep track on everything.

At the beginning of CIC training, I had guidance by my co-workers, so I could get used to the centre's dynamics. This was crucial to perform my activities correctly and in the right time. I learned that scheduling all CIC's events was imperative, in order to keep everything organized with antecedence. The reason of this is because unexpected situations occur all the time and, when it happens, it is good to have the expected ones under control.

The unexpected is indeed a keyword in clinical trial coordination. Even when everything is well prepared and anticipated, there can always be occasions beyond our control, for example, patients arriving late to the centre, delaying all procedures with different professionals (physicians, nurses, psychologists, etc.) that have tight schedules and other commitments; or when it is impossible to collect blood samples, for some reason, and it is necessary to reschedule another day to do it, without violating the timelines established by protocol. These are situations that need quick solutions. Fast thinking is required to take immediate actions to solve the problem, avoiding further complications. It is the most important quality of any SC and I am very proud to say that I managed to learn it, almost instinctively, during the five months. In my opinion, the will to adapt is fundamental in a professional experience like this and I think I adapted quite rapidly to this new way of working.

Another crucial point of my training as a SC was the responsibility that the job implies. It was not an obstacle or an evident difficulty, but I had to be aware that I was dealing with people, most precisely, with patients that need care and special attention. So, the consequences of possible mistakes and negligent acts would be severe and could result in negative impacts in patients' participation in the study. Therefore, I had to think and to act as a healthcare professional, i. e., I've managed to perform every task and activity, keeping in mind what decisions would be more convenient for patients' life, for example, when a patient had to go through many exams and evaluations, I tried to schedule everything to one single day, if possible, to avoid multiple visits to the hospital, which would be tiring to the patient and would compromise his professional life, if that was

the case. Even if that meant a little more sacrifice of our part. This was the first time during my internship that I felt I had fully responsibility of my actions, even though with a little guidance, unlike the pharmacovigilance training, where everything I did had supervision before its submission. I learned much with this type of responsibility. It helped me grow as a human being, giving priority to more important values.

Despite all obstacles and difficulties, working as a SC allowed me to have very positive experiences. Contact with patients was one of them. It was challenging but fascinating at the same time. All patients had their own peculiarity and I had to adapt my speech and behaviour for each one. It was difficult in the beginning but, with time, I gradually improved my communication skill. Actually, it was the best part of my whole internship, because I had the opportunity to have direct contact with the main reason this area of study exists: patients. It is for them that pharmaceutical research and development is made and it's because of them that I am so interested in it. Clearly, I knew this all along, but it was when I sit in front of a real patient, with a real disease that this became even clearer.

I would say that these five months working as a SC had a meaningful impact in my learning process. In the beginning, I interrupted many of my tasks to read and to ask questions, and I had some difficulties to communicate with patients. Also, everything seemed to happen at the same time and all seemed impossible to conciliate. I improved much in each day and I'm aware that, in the end, I was a better professional, performing my tasks fluidly, anticipating every event and communicating with patients with more confidence. These were the good things I took from this experience.

The next and final stage of my internship was not so challenging. Working in data management was a more pacific experience, compared to the previous one. Here, I had more time to think about the best way to perform the tasks I described earlier on this report, to search more information and to take a look at other databases and statistical analysis. It was exactly the opposite of the CIC's training: while there I had to think fast and take quick decisions, in data management, every decision was timely considered as well as every detail, in order to guarantee the quality of the work.

Constructing a database was a long and time consuming task but very interesting too. I've managed to elaborate tools to help me organize several data entries. This helped me improving my organizational skills. A well elaborated database facilitates its analysis and it is easier to consult, and that is what I tried to do. Also, I understood why activities like this take time and need concentration to perform.

The second task, where I had to perform a descriptive statistical analysis, also helped me to understand the importance of biostatistics in this area. I did this activity resorting to

what I learned from one of my master's module. As I described earlier, this was a basic task and it was not necessary to use advanced methods. Finishing the analysis was relatively easy. The challenging part was presenting the results. Creating a slideshow seemed a simple task, but it is necessary taking into account what is important to present and how to display those results in that presentation. At the first try, I simply pasted the results in as they were displayed by SPSS. But then I was told that the way we present the statistical results is very important. It is not enough to show the obtained data. In a presentation, it is crucial being able to show what it means and how it answers the study's questions. My skill in statistics did not improve substantially with this task, but it was good to test my knowledge in the area by doing it alone without any help. The main lesson here was the importance of it, when we intend to assess the quality of a study. If the results are negative, it is possible to end the study earlier than scheduled.

In overall, I can say that I was able to surpass almost every obstacle and difficulty. In addition, I could retrieve lessons from them and learn something important and useful for my future.

6. Conclusion

On the second year of my master's degree, I performed a 10-month curricular internship at the CPU. This report intends to illustrate that experience, to discuss what I learned from it and how I grew up as a future professional.

It was a unique internship because I had the opportunity to work in three areas of pharmaceutical medicine and experience different ways to embrace the problems and how to solve them. During the 10 months, I faced many challenges and obstacles. However, each one of them allowed me to improve my professional skills, such as organization, responsibility, communication, critical thinking, scheduling and working under pressure. These skills are what I treasure from the most difficult parts of the job.

Working on pharmacovigilance allowed me to understand the importance of the continuous evaluation of medicines to assure their safety. Also, I understand that everyone has an important role in this process, by reporting adverse events, contributing to clinical research. At CIC, I managed to comprehend the responsibilities of a SC and the importance of this role on the success of CTs. Not only because of the tasks they perform, but also the problems they solve and the complications they avoid. The contact with patients was one of the best experiences as a SC and a wonderful mark in my life. In data management training, I understood the importance of the back-office tasks and how it is crucial to have this side of clinical research constantly working and publishing data, from which will be possible to take conclusion and continue to improve pharmaceutical research and development.

These 10 months were a period of constant learning and growth. Compared to what I was and what I had before this internship, today I am a person who evolved in all levels, being more capable of developing new activities and accepting more challenges.

Everything I went through during this internship and what I learned from it was an exceptional way to complete my master's degree and to consolidate a whole year of training and formation. I would classify this internship as a positive mark in my learning process and a good starting point for my future career. I am conscious that the opportunity of working in a prestigious unit like CPU potentially opened many windows to begin a solid career. Now, it is my turn to avail the good things I took from the internship and look for other opportunities, in order to continue to grow and improve this professional journey, which began with this curricular internship.

7. References

1. IMM Lisboa — Organização [Internet]. [cited 2016 Mar 22]. Available from: https://imm.medicina.ulisboa.pt/pt/imm-lisboa/organizacao/
2. Instituto de Medicina Molecular. IMM Report 2013. 2013;
3. IMM. Faculdade de Medicina da Universidade de Lisboa | Sobre o Programa [Internet]. [cited 2016 Mar 22]. Available from: http://www.medicina.ulisboa.pt/ensino/formacao-avancada/programas-de-doutoramento/programa-de-doutoramento-do-centro-academico-de-medicina-de-lisboa-phdcaml/sobre-o-programa/
4. Instituto de Medicina Molecular. IMM - Scientific Report 2014. 2014;(March):180–201.
5. Milne MP. Unidades Regionais de Farmacovigilância como Aproximação aos Profissionais de Saúde Introdução. Unidade de Farmacovigilância do Norte - Faculdade de Medicina do Porto; 2004.
6. Hobart JC, Cano SJ, Zajicek JP, Thompson AJ. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. Lancet Neurol. 2007;6(12):1094–105.
7. Hobart J, Cano S. Rating Scales for Clinical Studies in Neurology — Challenges and Opportunities. Touch Briefings. 2008;12–8.
8. PPD. Clinical Research Basics [Internet]. Available from: http://www.ppdi.com/About/CRO-Overview/Clinical-Research-Basics
9. University of Virginia School of Medicine. What is Clinical Research [Internet]. Available from: https://research.med.virginia.edu/clinicalresearch/participate-in-a-trial/what-is-medical-research/
10. U.S. Food & Drug Administration. FDA - Types of Clinical Research.
11. Thiese MS. Observational and interventional study design types; an overview. Biochem medica [Internet]. Croatian Society for Medical Biochemistry and Laboratory Medicine; 2014 [cited 2016 Oct 19];24(2):199–210. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24969913
12. PHRMA. Biopharmaceutical Research & Development : The Process Behind New Medicines. 2015;1–21. Available from: http://www.phrma.org/
13. GlaxoSmithKline. How we discover new medicines | GSK [Internet]. Available from: http://www.gsk.com/en-gb/research/how-we-discover-new-products/how-we-discover-new-medicines/

14. MedlinePlus. Clinical Trials. National Library of Medicine;
15. National Institutes of Health. The Basics of Clinical Trials | NIH [Internet]. 2016. Available from: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
16. U.S. Food & Drug Administration. FDA - The Drug Development Process. Office of the Commissioner;
17. International Conference on Harmonisation. ICH GCP - SPONSOR [Internet]. Available from: http://ichgcp.net/5-sponsor
18. Profil Institut für Stoffwechselforschung GmbH. The phases of preclinical and clinical trials [Internet]. Available from: https://www.profil.com/knowledge-center/trial-stages
19. the balance. Contract Research Organization (CRO) Overview [Internet]. Available from: https://www.thebalance.com/contract-research-organizations-cro-2663066
20. Krishnankutty B, Bellary S, Kumar NBR, Moodahadu LS. Data management in clinical research: An overview. Indian J Pharmacol [Internet]. Medknow Publications; 2012 Mar [cited 2016 Oct 23];44(2):168–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22529469
21. European Parliament. Data Protection. a Guide for Users. 2015;
22. European Commission. Pharmacovigilance - Medicinal Products for Human Use [Internet]. Available from: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm
23. European Medicines Agency. Guidelines on good pharmacovigilance practices (GVP). 2016;
24. WHO | Fast facts on Pharmacovigilance. WHO. World Health Organization; 2015;
25. Hidalgo-Simon A, Arlett P. Pharmacovigilance in Europe: direction of travel in a changing environment. Expert Rev Clin Pharmacol [Internet]. 2012 Sep 10 [cited 2016 Oct 23];5(5):485–8. Available from: http://www.tandfonline.com/doi/full/10.1586/ecp.12.46
26. Nelson RC, Palsulich B, Gogolak V. Good pharmacovigilance practices: technology enabled. Drug Saf [Internet]. 2002 [cited 2016 Oct 23];25(6):407–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12071777
27. European Medicines Agency. Pharmacovigilance - Good pharmacovigilance practices [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

28. INFARMED IP. Portal RAM [Internet]. Available from: https://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
29. U.S. Food & Drug Administration. FDA - What is a Serious Adverse Event? Office of the Commissioner;
30. International Conference on Harmonisation (ICH), Nicholson A. Introductory Guide|MedDRA Version 19.1. 2013;(March).
31. Bellary S, Krishnankutty B, Latha MS. Basics of case report form designing in clinical research. Perspect Clin Res. 2014;5(4):159–66.
32. Skovlund E. Interim analyses in clinical trials. HeartDrug. 2003;3(2):113–6.
33. Cancer Research UK. Why are drugs so expensive? [Internet]. Available from: http://scienceblog.cancerresearchuk.org/2014/12/16/dances-with-pharma-part-1-why-are-drugs-so-expensive/