Universidade de Aveiro Secção Autónoma Ciências da Saúde
Ano 2014

Márcio Correia Barra

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 do Professor Doutor Joaquim José Coutinho Ferreira, Professor Auxiliar da Faculdade de Medicina da Universidade de Lisboa, e da Professora Doutora Alexandra Isabel Cardador de Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro.

o júri

presidente

Doutor José Luís de Almeida

Professor Associado Convidado da Universidade de Aveiro

Doutor José Carlos Fontes das Neves Lopes

Professor Auxiliar da Universidade de Aveiro

Professor Doutor Joaquim José Coutinho Ferreira

Professor Associado da Faculdade de Medicina da Universidade de Lisboa

Alexandra Isabel Cardador de Queirós

Professor Coordenador s/ Agregação

agradecimento

Gostava de agradecer a todos que tornaram o estágio possível. Em primeiro lugar, aos meus orientadores, Professor Joaquim Pereira e Professora Alexandra Queirós, pela sabedoria, paciência, apoio e orientação ao longo do estágio.

O meu sincero obrigado aos diretores do Mestrado em Biomedicina Farmacêutica, Professor Luís Almeida e Professor Bruno Gago, pela educação e pelas oportunidades nos últimos dois anos.

À Dra. Ana Noronha e à Dra. Maria Finisterra, a vossa companhia, conhecimento, amizade e apoio durante o estágio foram essenciais para o sucesso deste.

À Dra. Ana Teresa, Dra. Daisy de Abreu e Dra. Nilza Karina por toda a preciosa disponibilidade para ajudar.

Ao Dr. Daniel Caldeira, muito obrigado por tudo o que me ensinou e pela amizade.

Um obrigado especial à Ana Salgueiro e André Cardoso, pelas experiências ao longo do estágio.

À Bárbara Pinho, Daniel Silva, Daniel Cruz, Filipa Almeida, Diana Soares, Igor Marques, Isabel Magalhães, Inês Ramalho, Liliana Pinto, Maria Eduarda, Miguel Monte, Mike Costa, Raquel Costa, Rúben Alves, Tiago Silva, Vítor Vieira, Adriana Ferreira, Adriana Passos, Andreia Silva, a vossa amizade foi uma fonte de motivação.

Aos meus colegas de mestrado, obrigado por todas as esperanças e sonhos que partilhamos. Ao Dr. Eduardo Ribeiro, Dr. Rui Pedro Bento, Dr. Joaquim Fonsenca e Dr. Carlos Ribeiro, muito obrigado por toda a ajuda, discussões, e apoio ao longo destes dois anos.

À Anabela Farrica, por todo o companheirismo ao logo destes anos.

Aos meus pais, pelo incansável apoio e força.

palavras-chave

Coordenação de ensaíos clínicos, medical writing, ensaíos clinicos, estudos observacionais

resumo

Este relatório apresenta a minha experiência de estágio no Grupo de Neurofarmacologia Clínica da Unidade Neurológica de Investigação Clínica, onde pude desenvolver atividades de coordenação de ensaios clínicos, e no Laboratório de Farmacologia Clínica e Terapêutica, onde pude participar em projetos de investigação, essencialmente como *medical writer*. O estágio realizou-se entre 2 de Setembro de 2013 a 2 de Junho de 2014.

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

Neste relatório irão ser abordadas as atividades de coordenação de ensaios clínicos e estudos observacionais, bem como as atividades de *medical writer* que tive a oportunidade de desenvolver.

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 atividades de coordenação de ensaios clínicos e observacionais. Também tive a possibilidade de observar, ao longo do estágio, todas as dificuldades logísticas com que um centro de investigação se depara na condução de ensaios clínicos.

Na componente de escrita científica, tive a possibilidade de melhorar as minhas capacidades de escrita científica, perceber os processos necessários para a publicação de uma revisão sistemática e compreender algumas noções de meta-análises.

Em conclusão, o estágio permitiu-me pôr em prática o conhecimento adquirido na Universidade e serviu como nova fonte de aprendizagem.

keywords Clinical trial coordination, meta-analyzes, clinical trials, observational studies

abstract

This report concerns my internship experience in the Clinical Neuropharmacology Group of Neurological Clinical Research Unit, where I could work in coordination of clinical trials, and in the Laboratory of Clinical Pharmacology, where I could participate in research projects, mainly as a medical writer. The internship took place from 2 September 2013 to June 2, 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 the coordinating activities of clinical trials and observational studies, as well as medical writing activities.

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 observational trials. I also had the opportunity to observe, all the logistical difficulties inherent to clinical trials.

In scientific writing component, I was able to improve my scientific writing skills, to know how to develop a systematic review and understand some of the concepts of meta-analyses.

In conclusion, the internship allowed me to put into practice the knowledge acquired in the University, and served as an extremely valuable learning source.

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List of Abbreviations

AB Administration Board

ADR Adverse Drug Reaction

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

CHLN Centro Hospitalar Lisboa Norte (North Lisbon Hospital Centre)

CM Clinical Monitor

CNS Central Nervous System

CRF Case Report Form

CRO Contract Research Organization

CT Clinical Trial

eCRF Electronic Case Report Form

EU European Union

DCF Data Clarification Form

EC Ethics Committee for Health

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

GCP Good Clinical Practice

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

ICF Informed Consent Form

ICP Informed Consent Process

LCPT Laboratório de Farmacológica Clinica e Terapêutica (Laboratory of Clinical Pharmacology and Therapeutics)

IMM Instituto de Medicina Molecular (Institute of Molecular Medicine)

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

ICH International Conference on Harmonization

ISF Investigator Site File

IVRS Interactive Voice Response System

IWRS Interactive Web-Response System

NCRU Centro de Ensaios Clínicos de Neurologia (Neurological Clinical Research Unit)

NME New Molecular Entity

PI Principal Investigator

RCT Randomized Clinical Trials

SC Study Coordinator

SPC Summary of Product Characteristics

1. Introduction

For my second year of my Master's degree in Pharmaceutical Biomedicine, I undertook a 10-month Internship at the Laboratório de Farmacologia Clínica e Terapêutica Terapêutica (Laboratory of Clinical Pharmacology and Therapeutic - LCPT) of the IMM, comprised of a research unit focused on clinical trials of neurological disorders - Centro de Investigação Clinica Neurológica (Neurological Clinical Research Unit - NCRU), the Unidade de Farmacovigilância de Lisboa e Vale Sul do Tejo, and the Portuguese Branch of the Iberoamerican Cochrane Network. This internship was conducted under the supervision of Professor Joaquim Ferreira and Professor Alexandra Queirós. This document is the report of the internship, a summary of my experiences, activities and projects over these 10 months.

This introduction presents the objectives defined for my internship, details the structure of the hosting institution and provide an overview on the organization of this report to ease the reader's comprehension.

1.1. Objectives

The following objectives were defined in the beginning of my internship: Back in September 2013, when I first entered the hosting institution for the curricular internship, I had some goals on my mind of what I hoped the internship to be, what I could learn. The following are the goals for my internship:

- Acquire skills and qualification in the coordination of a clinical research centre;
- Gain awareness on all procedures and steps related to a clinical trial, including empirical knowledge on associated activities like clinical trial monitoring, and quality assurance;
- Improve my writing skills;

I also established some secondary objectives:

- Publish a peer reviewed paper;
- Improve my teamwork and communication skills;

To be able to reach the end of the internship with these goals fulfilled would provide me with a great sense of accomplishment. I knew from the beginning that a considerable amount of effort would be required to accomplish them, but I was more than willing to work hard and learn as much as possible from the experience.

1.2. Structure of the Host Institution

The internship was held in the LCPT unit of the IMM. The current structure of Laboratório de Farmacologia Clínica e Terapêutica comprises three distinct components: The Neurological Clinical Research unit, for conducting clinical and observational trials, and located on the 6th floor of the Neurology department of the Hospital Santa Maria, the Unidade de Farmacovigilância de Lisboa e Vale do Tejo (Pharmacovigilance Unit of Lisbon and Vale do Tejo) and the Portuguese Branch of the Iberoamerican Cochrane network. The last two are located on the Laboratório de Farmacologia (not to be confused with the Laboratório de Farmacologia Clínica e Terapêutica), a physical space located in the third floor of the hospital. The Laboratório de Farmacologia space is where a broad range of support activities for the NCRU and faculty projects occur. This location is mostly focused on management of investigator driven research, alongside statistics, medical writing, project management, and other support activities.

Most of my activities were held in the NCRU. This unit, established in 1999, is located on the 6th floor of the Neurology department of the Hospital Santa Maria, and it is where clinical trials and observational studies of new drugs for neurological disorders are conducted. The hospital has a long history with neurology clinical trials, and started to receive clinical trials through the efforts of Professor Antonio Damásio, and Professor Castro Caldas. Some of the trials that the neurology department received in the sixties include the Levodopa trials, the current gold standard for the treatment of Parkinson's disease(1), and selegiline, the first selective inhibitor of B-Type Monoamine Oxidase and the first synthetic catecholaminergic activity enhancer drug(2).

Back then, the NCRU was an independent unit from the LCPT, which was then called Instituto de Farmacologia e Terapêutica Geral, headed by Professor Virgilio Durão. The two units started to come together when Professor Cristina Sampaio was invited to work in both units, and an informal union was established.

Skip forward to the late eighties, early nineties, with Dr. Mario Miguel Rosa and Professor Joaquim Ferreira being invited to work in both units. The former eventually became the leader of the LCPT, when Professor Cristina Sampaio left the unit to become Chief Medical Officer of the CHDI Foundation. A then separate organism was created in 2001, the IMM, and these two units eventually ended up being integrated into the IMM.

Currently, through the efforts of Professor Joaquim, the NCRU became a part of the LCPT, independent from the Neurology Department (though it borrows a floor of the hospital) and under the IMM's authority. This unit also shares its space with the Portuguese Branch of the Iberoamerican Cochrane Centre, and the Unidade de Farmacovigilância de Lisboa e Vale do Tejo. Owing to this, the

work environment of this unit is very diverse, since you can find people with very different scientific backgrounds working together in close proximity.

The NCRU unit has participated in several multi-centre and multinational clinical trials consistently over the years. Since its creation, the NCRU had a total of 136 clinical and observational studies. These are spread across numerous neurological conditions, including: Parkinson's disease, Alzheimer's disease, cervical dystonia, Huntington's disease, multiple sclerosis, familial amyloid polyneuropathy, epilepsy and psychosis

Since it is located in the Neurology Department, the NCRU has great proximity to both patients that might be able to enter a clinical trial. Potential candidates are identified at the outpatient clinic of the Neurology Department of the hospital. The research unit can count with the support of experienced neurologists, psychologists, psychiatrists, and other healthcare professionals, who are essential for conducting clinical trials. There is also a close link with the department of clinical trials in the hospital pharmacy, which is responsible for receiving, storing, and providing the drugs used in the clinical trials. At the moment, the NCRU is scheduled to move from the sixth floor to the seventh floor of the hospital, in order to enjoy more space and expand its scope to other disorders, and not solely on neurology.

1.3. Report structure

The report is structured as follows:

- **Chapter 1 – Introduction**: in this section I identify the objectives of my internship, as well as provide a characterization of the host company (the history and the mission of the LCPT). The report structure is also presented to ease reader comprehension.
- **Chapter 2 – State-of-the-Art**: in this chapter, I provide some context for the activities in did during my internship. I introduce general concepts and procedures related to clinical research, the concept of what is a clinical trial and the current state of clinical trials in Portugal. I also discuss what medical writing is and detail what is a systematic review.
- **Chapter 3 – Developed activities**: this is the main chapter of this report where I present all the activities realized in my internship. An overall timeline of the internship is provided, and my experience working as a clinical trial coordinator is discussed. I also describe the projects I worked on as a medical writer
- **Chapter 4 – Discussion**: this chapter presents a discussion of the internship, alongside an overview of what I learned during these 10 months, and where could I improve upon. I also present my contributions to the hosting entities.
- **Chapter 5 – Conclusion**.

2. State-of-the-Art

My activities during the internship can be divided into two large groups: Clinical trial coordination, and medical writing. Clinical trial coordination was the main activity and the one where I spent more time. The theme is a complex one to simply start detailing what I did without any background, so it is important for me to provide some much needed explanations and context on what is a clinical trial, the goal of clinical research, and, seeing as it is a global activity, what is the current state of the activity in Portugal.

Clinical research in humans nowadays can be divided into two large groups: The first is the clinical trial. In a clinical trial, also known as an interventional study, participants receive a specific intervention according to the study protocol. The intervention can be a pharmaceutical product, a medical device, or a lifestyle intervention, like a diet. Clinical trials usually compare a new medical treatment to a comparable one that is already available on the market, or to a placebo that contains no active pharmaceutical substance. When comparing two or more interventions, clinical trials usually randomize the participants to receive a given intervention. If the participant does not know which treatment he is being given, the study is said to have a single-blind design. If neither the investigator nor the participant knows, then the study is called a double-blind study. Clinical trials are very useful since, for example, when a new pharmaceutical product is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives, including no intervention. Clinical trials help determine the efficacy and safety of new interventions through the measurement of endpoints, like for example, overall survival in a cancer treatment(3).

The second is the Observational studies, which involves the direct observation of individuals in their natural setting, without a direct intervention by the evaluator except for data gathering. As such, who does or does not receive an intervention is determined by individual preferences, practice patterns, or policy decisions, and not by random allocation of individuals (3, 4).

Seeing as my internship was mostly concerned with clinical trials, with very little involvement in observational trials, the state of-the-art chapter will focus on what is a clinical trial.

2.1. What is a clinical trial?

Clinical trials, as a concept, are relatively recent, although in the past various experiments were performed that could be passed off as clinical trials(5). This type of experimental research study emerged when it began to become apparent that a structured approach was needed to ascertain whether a drug was effective, or if its effectiveness was merely due to chance or other random factor.

British physician Dr. James Lind is deemed by the scientific community as the father of the clinical trial, as he designed and conducted what was the first clinical trial, in 1747. Lind, whilst working as a surgeon on the British naval ship Salisbury, was confronted by the high mortality of scurvy amongst the sailors. He selected 12 ill sailors and divided them into groups of 2, with all subjects displaying similar symptoms. Isolated from the rest of the crew, the men were given the same rations, but each pair was allocated to a different scurvy treatment: either cider, a weak acid, vinegar, sea-water, nutmeg and barley water, or oranges and lemons. The results were clear: Oranges and Lemons gave the most sudden and visible good effects (5, 6).

Move forward to the 20th century, with early clinical trial designs beginning to lean heavily on agricultural experiments, where randomization was employed to reduce bias by confounding factors, like soil characteristics and moisture. The work by RA Fisher in the 1930s led many, including Dr. Austin Bradford Hill, to design and adopt similar experimental designs in clinical trials, with the "British Trial" appearing in 1948(6). This was first widely publicized randomized clinical trial, which evaluated streptomycin for the treatment of pulmonary tuberculosis. The modern template of the clinical trial was here established, alongside the concept of a control, with the word 'control' meaning that the potential new medicine under investigation is compared with a 'control' group, which can be either placebo, no treatment, active control or different doses of the investigational drug(3). An emphasis on establishing key endpoints before the start of the study was another important concept brought forward by Dr. Austin.

A more contemporary definition of clinical trial is the one employed by the International Conference on Harmonisation (ICH) Good Clinical Practices E6 guidance(7), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. This guidance states, that a clinical trial is "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. "[(7), p.3)

Clinical trials can be distinguished into 4 phases(7): human pharmacology trials, or Phase I studies, therapeutic exploratory trials, or Phase II studies, therapeutic confirmatory trials, or Phase III trials and therapeutic use study, or Phase IV trials.

In human pharmacology trials, or Phase I studies, are typically carried out in healthy volunteers, and it is here where the drug is administered for the first time in humans. The goal is to determine the tolerance, pharmacokinetic and pharmacodynamics profile of the experimental drug, before it is

administered in patients. Safety of the drug is the priority in this phase, with efficacy evaluations being done in the following phases.

The primary objective of therapeutic exploratory trials, or Phase II studies, is to explore the therapeutic efficacy in a small number of individuals with the target disease. The use of the drug for the targeted indication is explored, and a dosage or dosage scheme is estimated. Preliminary efficacy and safety information is obtained, and the foundations for the pivotal phase III trials are placed.

Therapeutic confirmatory trials, or Phase III trials, are trials which are conducted in a large pool of patients, with the goal of exploring the efficacy and safety of the exploratory drug in treating a given condition. This type of study provides the basis for the assessment of the benefit/risk relationship, and to gather enough information to submit to regulatory authorities for drug approval.

The last phase, therapeutic use study, or Phase IV trials, concern to trials which are done after a drug has obtained marketing approval. In the therapeutic use study, the objective is to refine the understanding of the benefit/risk relationship, to further explore the use of the drug in special populations or conditions, and gather a wider sense on the safety of the drug, with a special focus on rarer adverse events which might have not been detected in previous phases.

Seeing as clinical trials are a highly specialized field of work, it is not surprising that they demand very capable individuals to work in teams. The clinical research team is a multi-disciplinary work force, tasked with properly conducting the clinical trials in a research centre. A clinical research team is comprised by the following team members:

- Investigators and sub-investigators, who are physicians with proper training and experience in conducting clinical trials. They are responsible for recruiting participants, providing adequate medical care to clinical trial subjects, ensuring the safety and well-being of the patient during the clinical, prescribing and administering the investigational product, and resolving queries from the clinical trial.
- The clinical trial coordinator is an integral part of the research team. Working under the investigators, this professional is responsible for conducting the study in accordance with the protocol and the ethical standards that govern clinical research. As a coordinator of the study, the clinical trial coordinator oversees a number of different tasks, with general administrative being the majority. The clinical trial coordinator might also handle financial aspects, oversee personnel, and many others. Aside from this, the clinical trial coordinator is also in charge of preparing and filling important documents, like budget proposals, audit reports, training documents and case reports. This professional also eases the entire

research process, by monitoring the procedures, collecting data and many other procedures, acting as a "glue" throughout the entire process.

- The study nurse, who is responsible for collecting biological samples from the participants, as well as giving overall support to the study team.
- The hospital pharmacy and the hospital pharmacists, who are responsible for receiving, storing, dispensing and for the accounting of the investigational product.

Considering the variability of clinical trial activity, and multidisciplinary professionals involved, the legal framework surrounding clinical trials is also complex and includes a long list of documents, guidelines provided by regulatory agencies, and overarching ethical guidelines. All clinical trial professionals have to know, at least, the following guidelines: The Helsinki Declaration(8), the ICH-GCP E6(7), Directive 2001/20/CE(9), Directive 2005/28/CE(10), and Directive 95/46/CE(11).

These documents establish the ethical guiding principles for conducting clinical research and the necessary guidance to ensure that clinical research is standardized in the world (in the case of the ICH-GCPs), and throughout Europe (in the case of the directives). Ethical guidelines exist due to both historical reasons and ethical reasons. Throughout history, many experiences which could be passed of as clinical trials were conducted in unwilling participants, without their authorization, and in inhumane conditions. The many ethical principles that exist nowadays, with the most important ones being the Helsinki Declaration and the ICH GCPs, were created to ensure that all clinical research is conduct in willing participants, who were previously informed of the potential risks and benefits of a given intervention, and gave their informed consent. Above all, these documents ensure that the wellbeing of the participant is above anything in a clinical trial(12).

The Helsinki Declaration(8) was one of the first documents to set the foundations for ethical treatment of clinical trial participants, following the Nuremberg Code established in 1947 after the atrocities committed in World War 2 by the Nazi regime. The Helsinki Declaration specifies a series of ethical principles for medical research involving human subjects in clinical trials. The first version of the declaration was adopted by the 18th WMA General Assembly, Helsinki, Finland in June 1964. The declaration has been amended seven times since, with the most recent version being adopted at WMA General Assembly in October 2013(13).

The ICH-GCP E6(7), Good Clinical Practices document details the responsibilities of each participant of a clinical trial, from the sponsor, to the investigator and the clinical trial coordinator, amongst many others. The final version of this document, issued in 1996, is a very detailed essay covering all the aspects of clinical trial research, in an effort to standardize clinical research in all three ICH regions: the United States of America, Europe, and Japan.

The current document governing clinical research in Europe is Directive 2001/20/CE(9), April 4th, also known as the clinical trials directive. This directive specifies the requirements for the conduct of clinical trials in the EU. This directive was transposed into the Portuguese national law by the Decree-Law 46/2004 of August 19th(14). It's "companion" document, Directive 2005/28/CE, April 8th(10), 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(15);
The last piece of regulatory legislation is Directive 95/46/CE(11), October 24th, concerning the protection of patient data. This directive was transposed to national law by ordinance nº 67/98 "Personal data protection"(16) and by Resolution nº333/2007(17), this one regarding personal data protection in clinical trials with medicines for human use.

2.2. Setting up and running a clinical trial

While the introduction might have provided some historical context on what is a clinical trial, the procedures for setting up and running a clinical trial also deserve an explanation, seeing as they were the cornerstone of my internship. A brief overview on the procedures for setting up a clinical trial will be now provided.
Every trial in the centre begins by a sponsor first having a new trial, for which it is interested in bringing to a number of centres in Portugal. A number of potential centres where the clinical trial could be held are selected to check if they are feasible to conduct the trial. Then, the feasibility process occurs. The objective of a feasibility process is to review the adequacy of the site, the training and experience of the study staff, the access to the right patient population, and the site's interest in the study. If a centre meets the needed requirements to conduct the trial and shows interest in conducting it, the feasibility evaluation is complete and the centre is eligible to enter the trial. This team usually includes a Principal Investigator (PI), a Sub-Investigator, a study nurse, a study coordinator, and other professionals, according to the requirements of the trial. If, for example, a trial has medical scales on its list of core assessments, a rater might be assigned for this task, who can be a psychologist or a physician.
After the feasibility, a study initiation visit follows. In this visit, a team of representatives of the sponsor come to the clinical trial centre, and provide an explanation of all trial procedures to the clinical trial team. This meeting is very important, as it brings both the clinical trial team and the sponsor under the same roof, face-to-face, and any urgent doubts that the team might have are answered by the representatives. When the centre is ready, it is then free to start recruiting patients for the clinical trial.

Like every other trial, the first time that a patient is proposed to enter a clinical trial by a physician, usually the PI, or a physician who is aware of the trial, the patient first receives an explanation of what the trial is about, and then receives a copy of the informed consent to take home. This is called the pre-screening visit. The patient is advised to read carefully the informed consent form, write any doubts and questions, and discuss with family members. If the patient then wishes to proceed and enter the trial, an appointment is scheduled for the signature of informed consent alongside the PI, and to proceed to the screening visit. The screening visit is where the patient is thoroughly evaluated to see if he/she fits all the inclusion and exclusion criteria. If, by the end of the screening, the patient does indeed fit all criteria, the patient then moves to the baseline of the trial. If trial is carried in a randomized, usually double-blind manner, the patient is randomized to one of the possible treatment arms.

After the patient is randomized, and given the treatment he/she was allocated to, the patient then enters the treatment period of the trial. The treatment period can either be very long (as in years), as in the case of treatments for chronic diseases, or very short, like, for example, phase II trials (months). During this period, the patient has to come to come to the centre in a regular basis (the periodicity of which depending on the trial), to attend medical appointments and for data on the treatment to be collected. The nature of the data that is collected, again, depends on the trial. Checking patient's compliance with the trial's procedures, health status, drug accountability, and many other procedures usually happen in these appointments.

If the patient reaches the end of trial, two options can occur: either he/she enters in a follow-up of the study, where the experimental drug is given in an open-label fashion, usually until the pharmaceutical is launched for sale. Open-label extension studies provide the patient the opportunity to receive the experimental pharmaceutical without any kind of blinding procedure, especially patients who were randomized to placebo. Moreover, providing the study drug over a further, more prolonged observation period may disclose adverse effects that were not observed in the original randomized clinical trial(18).

The patient, however, might not reach the end of the trial. As stated in the informed consent form, the patient is free to leave the trial anytime. In other cases, the patient might suddenly no longer fit the inclusion or exclusion criteria, or might take prohibited medication alongside the experimental treatment. An adverse event might occur while taking the experimental medication or a female participant might become pregnant. Prohibited medication is another concern, and the patient is provided with a list of pharmaceuticals that we will not be able to take while participating in the trial, mostly due to safety concerns.

Throughout this entire process of patient screening, randomization, treatment, and trial closure, the trial coordinator is a constant presence, and one of the upmost importance. This professional is an essential support member in the clinical trial field, by ensuring that everything is properly coordinated, documented, properly stored, and by providing support to the entire clinical trial team. Clinical trial research is a worldwide venue. One of the biggest databases for clinical trial, ClinicalTrials.Gov, lists, as of June 2014, 167456 studies with locations in all 50 states of the United States of America, and in 187 countries. Clinical trials make up the majority of registered studies, with 80% of the over 160000 studies being clinical trials, with the remaining 20% being observational trials(19). Since clinical trials are essential to obtain regulatory approval of a new drug, pharmaceutical companies place great emphasis on conducting clinical trials. The USA have been long the country with the highest number of clinical trials occurring. In Europe, Germany, France and the UK are the biggest players in the clinical trial field, attracting many clinical trial for their research centres. As for the emerging markets, China takes the top spot, with the country seeing nowadays more than 3000 trials underway, a large proportion of which are sponsored by global pharmaceutical companies(20). While research expenditure during the last few years has decreased, owing to the financial crisis that hit the main economic regions(21), new potential therapies continued to emerge, bringing with them clinical trials to a host of clinical research centers all over the world years(19). And so, where does Portugal stand?

2.2.1. State of clinical trials in the world and in Portugal

When looking at the clinical trial activity worldwide, growth has been a constant. Data from Clinical trials.Gov show that the numbers of clinical trials that is registered in the database has been growing each year. From 2010 to 2011, 18,226 new clinical trials were registered in this worldwide database. Similar growth was observed from 2011 to 2012, with 19,627 new clinical trials. From 2012 to 2013, 20,360 new trials were registered, and lastly, from 2013 to 2014, 21,239 new clinical trials were registered. Unfortunately, this tendency is not observed when looking at Portugal (19).

I started my internship in clinical trial coordination at a critical time for the clinical trial activity in Portugal, and I feel it is important, for the purpose of this report, to provide some background on clinical trials in Portugal, and what is their current state, especially when compared to similar sized countries. The clinical trial activity in Portugal has been decreasing at a steady pace. The number of ongoing clinical trials in Portugal between 2006 and 2012 decreased 26%, from 160 to 118 studies, with the lowest number of clinical trials ever submitted in Portugal being 2011, with only 88 studies. 2013 saw 114 trials being submitted for approval(22). The rate of clinical trials per million inhabitants in Portugal is among the lowest in Western Europe. Phase 3 and 4 trials make up 80% of

all trials, with phase 3 trials alone being responsible for 65% of trials approved in 2013(22). As for the phase 1 trials, these have almost no representation, with only 27 approved over the last 5 years. It is also troubling to see that the three companies with the greater number of trials are responsible for nearly half (41%) of all trials conducted in Portugal(22). Placed against other EU countries, these numbers are very poor.

Clinical trials by initiative of investigators are also few and far between, especially when compared with Spain and the UK, countries where academic clinical trials make up about a quarter of the total authorized trials in a year. Absence of legislation that regulates and promotes academic research is hurting this sector in Portugal(23).

When evaluating the process of new trial approval, Portugal pales in comparison against other European countries. The average approval time of a clinical trial exceeds 70 days. This average does not include approval by the institution where the trial is to be conducted, which can take several months. The real-time approval of a clinical trial often takes 6 months in Portugal. 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(23).

In a survey conducted by APIFARMA (Figure 1) in 2009 to ten pharmaceutical companies who conduct a significant portion of the clinical trials in Portugal, the number of active clinical trial in Portugal was lower than Austria, Belgium and the Czech Republic (countries with a similar number of inhabitants)(24).

Country	Number of active clinical trials	Number of planned sites	Planned patient recruitment	Investment (in millions of euros)
Portugal	147	461	3917	58755
Austria	188	596	5602	97530
Belgium	328	1.024	12996	194940
Czech Republic	218	967	15433	231495

Table 1 Clinical trials in Portugal, compared to similar EU member states(24)

With the lower number of trial comes lower investment from sponsors. Portugal lost 136 million of euros in potential investments, compared to Belgium.

Another study from APIFARMA, still in progress, with data collected from 443 clinical trials conducted in 2007 to 2011, shows light on how much money was planned to be invested in Portugal

versus the money that was actually invested. The still preliminary data shows that 14 million euros were lost in that period, mostly from unsatisfactory patient recruitment(24).

In July 2013, PwC, in Partnership with Apifarma, released an in depth report entitled "Ensaios Clínicos em Portugal". The report detailed the clinical trial activity in Portugal and investigated its importance in the Portuguese economy, identify the main barriers to their progress and outline a set of proposals to overcome these limitations(23).

The study came in a critical time for the clinical trial industry in Portugal. The transposition of the current European Directive for clinical trials was already recognized as one of the main factors of loss of efficiency in the European Union and inequality between Member States. The March 2014 review of the Community legislative framework was a window of opportunity for Portugal to revamp its clinical trial structure, and communication between all stakeholders is absolutely necessary in the coming times(25). The report identified the five main obstacles for the clinical trial sector in Portugal: Politics and strategy, policy and legislation, organization and infrastructure, incentives and training and last, technology and information.

Despite all these shortcomings, this activity is still highly profitable for Portugal. The 370 active clinical in trials in 2012 had a market value of 35 million euros, and 7.5 million in tax revenue. Clinical trials also saved 3.5 million euros in expenses in medicines for the Portuguese Government. The clinical trial activity was responsible for a Gross Value Added of 72 million euros in 2012. For each euro that is invested in clinical research, it is estimated that there is a return of 1.98 euros for the Portuguese economy. This makes clinical research one of the activities with the highest return on investment in the country. Thus, in the middle of austerity, this activity should be higher on the priorities of the country.

The lack of interest from sponsors to conduct clinical trials in Portugal is harmful to the country and its economy. The direct (and indirect) impacts of clinical trials in a country's economy are very significant (23, 24, 26)**:**

- They contribute to the budget of a state, through paid taxes.
- Provide alternative cost savings.
- An additional mechanism of remuneration to investigators.
- Employment opportunities, additional work for researchers and young physicians and economic stimuli for other supporting business.
- Improved access for patients to better treatments; usually sponsors provide more intense care and therapy for a clinical trial patient than what a normal patient gets under the standard healthcare system. Sometimes patients can't even afford the drug when it's released in the market, but volunteering in a clinical trial can make it accessible.

- Knowledge sharing and transfer of new technologies. Potential spillover effect to other areas of healthcare.

Portugal could certainly find these contributions useful in the current economic circumstances. Efforts should be done to motivate pharmaceutical sponsors to invest in Portugal and conduct clinical trials here. GSK, Lilly, and recently Pfizer closed their clinical research units in Portugal, which shows that big sponsors are simply not interested in investing in Portugal. The absence of a strategic vision for the activity of clinical trials, a legislative and regulatory framework that is inefficient and the inadequacy of available infrastructures to the needs of the clinical trial activity, has led Portugal to lose competitiveness in this sector. The successive drug price cuts that have been instated over the years naturally constitute a factor which discourages investment for research and commercialization of new medicines in Portugal(23).

It is in this scenario that I started my curricular internship in clinical trial coordination. I was no doubt curious to see how my knowledge of clinical trials, gained over these last 4 years as a university student, translated to the real world. I also set out to, even if little, make a difference during my internship, and provide something of value to the hosting institution, and to the clinical trial activity as whole in Portugal.

3. Developed Activities

My internship can be divided into two phases. In the first phase, which lasted from the start of the internship, in September 2013, until November 2013, I worked in the Laboratório de Farmacologia Clínica e Terapêutica in a series of medical writing projects, mostly concerned with cardiology topics. In the second, I started working in the NCRU, directly working as a study coordinator for the centre, while also remaining active in medical writing and other academia research projects. During this phase, my work was mostly focused on the EXPAND clinical trial, while also providing support in other clinical and observational trials.

Besides clinical trial coordination and medical writing, I also had the opportunity to participate in a series of parallel projects in the hosting institution. The hosting institution was also very generous in allowing and encouraging me to participate in some of the formative events that were held in the faculty of medicine and in my university. These will also be described in this report.

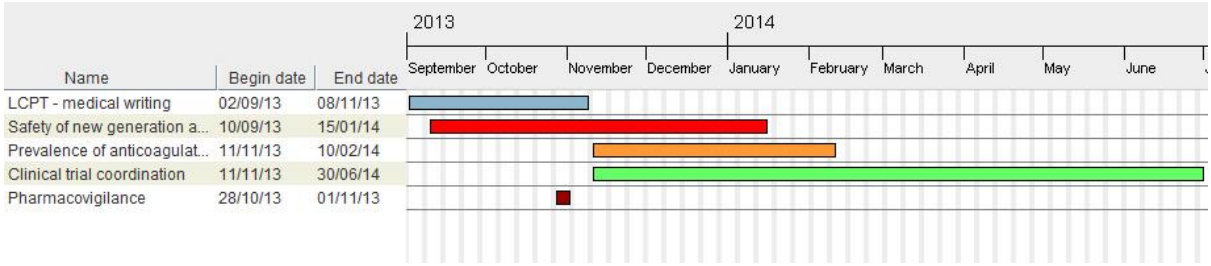

Figure 1 Gantt chart of my internship, showing the schedule of the activities

3.1. Introduction and training to the tasks of a Clinical Trial Coordinator

I began working as a clinical trial coordinator trainee in the NCRU in December 2013, after two months on the LCPT. In the NCRU, I worked under the close guidance of Dra. Ana Noronha and Dra. Ana Maria Finisterra, and alongside my colleagues from the master's, André Cardoso and Ana Salgueiro. It is worth noting that during the first week of the internship, I worked on the NCRU, and only after the first week was I transferred to the LCPT. Many of the things that happened on the first week were some of the most memorable, seeing as it was my first time seeing them. A good example was my first screening visit, a patient that was expected to enroll in a trial for a cervical dystonia treatment. It was at this point that I could see first-hand the amount of inclusion and exclusion criteria that even an admittedly simple trial such as this one could have.

The first week of the internship I received training from Dr. Ana Noronha and Dr. Maria Finisterra. I received a full overview of the clinical trial site, the procedures in place, where the material was stored, and the general workflow of the centre, amongst many others. One of the main focuses of this initial week was communication. Since I was in a completely new environment, I spent the majority of the first week asking questions related to the procedures, and receiving important feedback on my work. The hierarchical structure was also explained, and who were the different principal investigators of each trial. Every team member had very specific roles, which I had to become acquainted with.

Throughout the internship, I was given a lot of training in areas that are universal to almost all clinical trials. These included: compliance with the procedures stated in the protocol, measurement of vital signs, processing of laboratory samples, archiving and filling electronic Case Report Forms (eCRFs). What follows is a list of the more simple procedures where I received training during the initial days of the internship.

3.1.1. Compliance with the procedures stated in the protocol

Compliance with the investigation protocol is of the upmost importance, as to ensure that the results collected during the trial are accurate and scientifically sound. Before doing any of the trial procedures, I was required to read the protocol to gain an understanding on the objectives of the trial, the evaluations required, the schedules, and the study's procedures. Once I had shown to understand the protocols of the studies, I was able to collaborate in the visit procedures of the several clinical trials. After the investigators find a potential candidate to undergo a pre-screening visit, they would provide the research centre with the contact of the individual. I then received training in scheduling the screening visit with the patient or with his caregiver, taking into consideration the timelines required by the protocol and the participant's availability. For the remaining visits, usually these would be scheduled either by the investigator, or by the study coordinator, again, deepening on the protocol's timelines. For each visit, I was instructed to read what did the protocol require, and prepare accordingly.

3.1.2. Measurement of vital signs

All trials which were occurring in the centre required the measurement of vital signs in some schedule visits. The clinical trial coordinator is authorized to do these tasks, and so, I received training in measuring vital signs, from blood pressure, pulse, temperature to respiratory rate. This allowed me to do these simple procedures whenever the protocol required.

3.1.3. Processing of laboratory samples

Each study had a laboratory manual, providing instructions on how to collect, handle, process, and ship the required biological samples Human biological samples including organs, tissues and biofluids such as blood, and their derivatives, are increasingly important resources for biomedical research, as they provide very important data during the conduct of a trial (27). In our research center we only working with blood samples. Dra. Ana Noronha and Dra. Maria Finisterra taught me how to correctly handle the laboratory kits of each trial, how to work with the centrifuge as to process the samples according to the requirements, and prepare each sample to be shipped to the central laboratory, either in ambient temperature or in dry ice.

3.1.4. Archiving

Each study had a specific cabinet, where their documentation was safely archived. Each cabinet had a specific organization, but the basic features were similar for every trial, like patient dossiers, where all documentation of a clinical trial participant is kept, and the investigator dossier, an enormous file where all information concerning the clinical trial is available, including the study protocol, contact

information, financial agreements, study manuals, and much more. Organization is very important in clinical trials, as the tremendous workload and paperwork leaves a lot of opportunities for confusion to happen if the trial documentation is poorly organized, not to mention the risks of losing or misplacing documents. It was of the upmost importance to keep everything organized, in place, and readily available. If a document is lost, it means that information is lost and can never be recovered. This is very frowned upon by the clinical trial sponsor, as it showcases that the clinical research centre might have organizational issues.

3.1.5. E-CRFs

During the internship I had to learn how to handle different types of trial specific eCRFs. eCRFs are an electronic data collection tool provided by the clinical trial sponsor for the centre to collect data on the trial. All data on each patient participating in a clinical trial are required to be documented in the CRF. Each eCRF had its own layout, design, specifies, and quirks. Some eCRFs were more complex than others. Some were very intuitive, usually the modern ones, who placed a great deal of care on a friendly user interface, but others required timely checks of the eCRF manual to clarify doubts, or were very annoying to deal with due to the frequency of which they crashed. Throughout the internship, there were many queries that required prompt resolution. Simple queries, like data entry errors, were quick to solve, but more complex ones, like the ones related to inconsistences or incoherencies required a team effort amongst physicians and coordinators to be solved. The importance of data confidentiality when accessing the different eCRFs was also made clear during the initial training.

3.2. Trial specific activities

After my initial training in the tasks of the NCRU was concluded, I was in a position where I could start being a part of the larger activities in place at the centre. A large number of trials was already ongoing when I started the internship, and some of them started during the internship. The initial training was essential so I could do an efficient job on the clinical trial specific activities, such as preparing patient appointments and answering queries. While each trial is different, there are many features which are the same for all of them. What follows is some of the more specific, trial related activities I did.

3.2.1. Site initiation visit (SIV)

I was allowed to see two trial initiation visits in the Internship. These are formative events conducted by the pharmaceutical sponsor to prepare the research centre for the proper conduction of a trial. The entire research team is reunited, and the sponsor provides a presentation on the clinical trial, giving an in-depth look at the:

- The Investigator's Brochure (IB)
- The protocol, its goals and procedures
- Informed Consent Process (ICP) and Informed Consent Form (ICF)
- Investigational Product characteristics and handling requirements
- Adverse Event (AE) / Serious Adverse Event (SAE) reports
- Investigator Site File (ISF)
- Case Report Form (CRF)
- Source documents, documents where the trial specific information is collected
- Monitoring requirements and a tentative schedule

It is also an opportunity for the research team to ask all the questions concerning the trial that they might have, since occasions where the entire team is reunited in the same room, face to face, alongside representatives of the sponsor, are rare during the trial. After the presentation is concluded, I provided help to my fellow coordinator colleagues and the clinical trial monitors, by organizing the study dossiers in the cabinet, seeing if the delegation log was properly signed, and requesting signatures in cases where a member of the research team could not attend the SIV. Typically, after the SIV has been concluded, the site is ready to start recruitment. In some cases, an authorization by the sponsor is required, or, the recruitment is postponed until trial essential equipment arrives at the site.

3.2.2. Preparing patient appointments

Before each patient appointment, I had to study the core assessments of the visit, and the previous visits and history of the patient. Each appointment was scheduled by phone a few days before it, and in the phone call I reminded the patient to come fasted (if applicable) and to bring his patient diary (if applicable too).

A day or two before the visit, I pulled all the required material for the visit from the study cabinet, like the patient's medical file, the source documentation, IVRS or IWRS sheets, vital sign form and pharmacy prescription forms. I also prepared the laboratory tubes, pre-labelling them with the patient's identification.

3.2.3. The day of the appointment

For screening visits, I provided support to the principal investigator in the Informed Consent Process. While the Investigator provided the medical and scientific background of the trial, alongside all the medical evaluations required, my tasks were usually related to answering more logistics related questions that the patient might have, like for example how was transportation handled, where were the different appointments and evaluations, and precautions like taking care of the patient's diary. For visits of patients who were on treatment phases, I also received the returned medication and returned it to the hospital pharmacy.

While the investigator evaluated the patient, I completed the IVRS or the IWRS, depending on the visit, under supervision of Dr. Ana Noronha or Dr. Maria Finisterra. In visits where the investigational drug was dispensed, I filled the pharmacy prescription form with the medication lot number, the investigator signed and dated, and then I would send to the pharmacy through e-mail. The medication usually came 20 minutes after the request. Once at the centre, the investigator delivered the medicine to the patient, and provided instructions on taking it. Details on the next appointment would also be provided.

Once the Investigator finished with the examination, I measured and recorded vital signs under supervision of Dr. Ana Noronha or Dr. Maria Finisterra, performed the ECG and took the patient to collect biological samples. After the blood and urine samples were collected according to the laboratory specific study procedures, these were processed. This usually meant allowing some time to pass for the blood to clot, and then centrifuging the tubes. After centrifuging was over, I transferred the plasma to the transfer tubes. Some trials required smear preparations to be done, while others required urine samples, which I either requested the patient to bring beforehand to the visit, or to collect at the research centre. Once all samples were processed, I prepared them for shipping in the proper boxes. For visits which required samples to be sent in dry ice, I usually requested them in advance, as to arrive at the same day of the visit. Once the shipment was ready, I called the courier services to schedule the pickup.

For patient expenses, the research centre asked patients to bring receipts of the expenses, so that we could reimburse the patient.

3.2.4. Once the visit was over

After the visit came to a close, I reviewed all source documents, to make sure that all necessary data was collected, and then proceeded to enter it on the eCRF. If an ECG was done on a given visit, I would send it to the central lab for evaluation. All material used was archived properly on the patient's folder. Usually, after filling the eCRF with the collected data, some queries would appear.

Prompt resolution of queries was a must, so I would usually contact the investigator, or the concerned health professional, asking for a clarification.
Checking the laboratory material was also a common procedure, to ensure that the centre was well stocked for the upcoming visits.

3.3. The EXPAND trial

Shortly after I began working full time in the clinical research unit, I helped mostly on the EXPAND clinical trial, under the supervision of Dr. Ana Noronha and Dr. Maria Finisterra, while also providing support for other trials, and continuing to work on projects of the Clinical Pharmacology Laboratory.
The EXPAND trial (**Ex**ploring the efficacy and safety of siponimod in **pa**tients with Seco**nd**ary Progressive Multiple Sclerosis, CBAF312A2304) is a Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled study sponsored by Novartis. Approximately 1530 individuals, aged 18–60 years with Secondary Progressive Multiple Sclerosis will be randomized, either to Siponimod or to Placebo. The study's primary objective is to demonstrate the efficacy of siponimod relative to placebo in delaying the time to 3-month confirmed disability progression as measured by EDSS, a common method of quantifying disability in multiple sclerosis and monitoring changes in the level of Multiple Sclerosis disability over time (28, 29).
Other secondary outcome measures include the efficacy of siponimod relative to placebo in confirmed worsening of 25 foot walk test, efficacy in reducing the increase in T2 lesion volume, overall response rate on the MSWS-12 and number of adverse events, amongst others.
This was an incredibly complex trial to coordinate, owing to the design of the study itself, and to the very specific population that the study specified for inclusion. From preparing medical appointments of the study, providing backup, carrying equipment, receiving monitoring visits, managing the patient's appointment calendar, handling transportation requests and help filling the eCRF, the spectrum of activities that I did while working on this trial was very broad. For this trial I organized all paperwork in visits, as I believed that having all paperwork of a visit readily available would make the patient's history much easier to follow, and help the monitor's work. This was warmly received by the monitors.
One of the materials I created for this trial was a complete checklist with all visit procedures indicated per protocol for each visit, for each patient, with the dates of all appointments being added as the trial went along. I did this to make sure that all the correct clinical trial procedures were done in an appointment. Seeing as the trial is a very complex one, these were very helpful when planning the appointments, which were very time consuming, with a lot of procedures required and the participation of a sizeable number of team members. Visits usually would have to

be scheduled a week or two in advance, and in visits where a lot of team members were necessary, scheduling was usually a considerable challenge. A tight organization was also necessary to be as time efficient as possible, since long visits are very tiresome for the participant.

3.4. Activities as Medical Writer

For the first two months of the internship, I worked on LCPT on a variety of projects, most of them related to systematic reviews and meta-analysis on cardiology topics. When I was transferred to the NCRU, I still remained active on some projects of the LCPT. The following sections will first provide an overview on what is a systematic review and a meta-analysis, then I will detail all activities that I performed as medical writer.

3.4.1. Why are systematic reviews important in clinical research

To begin describing what the concept of a systematic review is, it is useful to first go through what is a review paper. Review articles are articles published in peer-reviewed journals that offer a summary of the current state of knowledge of a topic. It is generally agreed that reviews are a critical resource for practicing clinicians and healthcare professionals in keeping up-to-date with the rapidly expanding medical literature (30).

Reviews can be either narrative reviews, reviews that often just focus on a subset of studies and don't involve a complete search of the literature (ending up being more descriptive articles), and systematic reviews. Review articles are useful resources for physicians, but traditional narrative reviews often include a selective summary of research findings mixed with personal opinion, limiting their evidence. Systematic reviews have a broader approach, and possess many advantages over traditional reviews. These include the use of systematic and explicit methods to search for papers, to minimize the bias in identifying, selecting and summarizing the evidence (31).

In a systematic review a very thorough, systematic search of the literature is conducted, with the goal of being as informative, and with the less amount of bias, as possible (31).

A successful systematic review needs a previously stipulated search plan, designed to cover all relevant articles on a given topic. Every study that is pertinent is identified, appraised and synthesized. The end result of a systematic review is a summary of the best available evidence concerning a given treatment option. It is common for a systematic review to include a meta-analysis component, where statistical techniques are employed to synthesize the data of all included studies into a single quantitative estimate or summary effect size. These are particularly helpful when, for example, you have different studies with contradictory results. Pooling the results into a

single, unified result, can often lead to findings of significant clinical importance, with some systematic reviews leading to significant changes in clinical practice.

Throughout the world, there are several organizations fostering systematic reviews. A good example is the Cochrane Collaboration, a widely recognized and respected organization that promotes and disseminates the development of systematic reviews and meta-analysis (32).

Systematic reviews are, at the moment, one of the foundations of evidence-based medicine. Evidence-based medicine is the thoughtful and explicit use of the current best evidence when making decisions concerning the healthcare of individual patients (33). Seeing as systematic reviews provide a thorough sum of the best current evidence available, they are typically ranked in the literature as the best source of evidence, directly above randomized clinical trials (Figure 2)(34, 35), and are used by many regulators throughout the world for coverage and payment decisions (36).

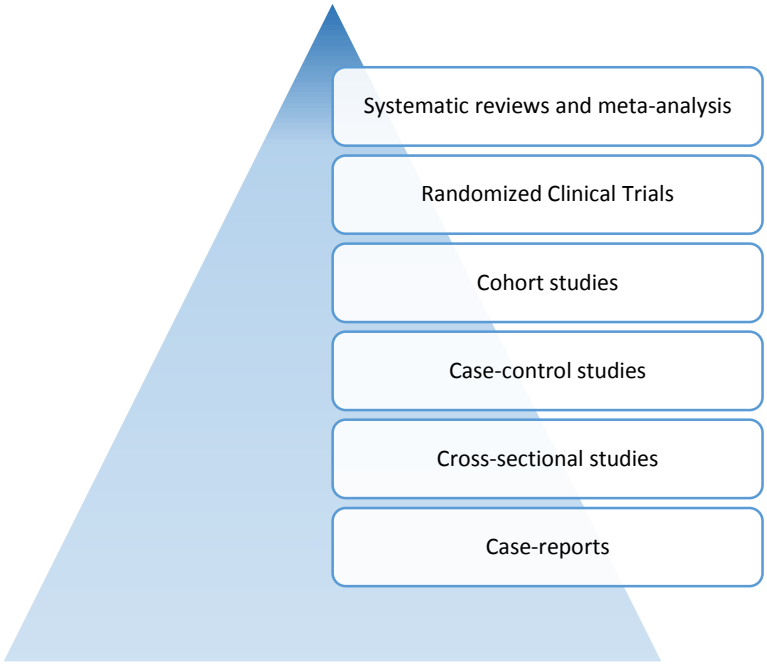

Figure 2 – Hierarchy of evidence (adapted from the UK's National Institute for Health and Care Excellence)(35)

When I was introduced to the LCPT, I was informed that I could help with Dr. Daniel Caldeira in his investigation projects. In my first days at the LCPT it was immediately made clear to me that all professionals working in the unit placed a great deal of importance in evidence based medicine. Dr. Daniel Caldeira was very eager to have someone who could help him in his systematic reviews, which were cardiology focused. This offered a nice contrast to the more neurology-centric projects found on the NCRU, and an opportunity to be able to publish something of relevancy during the

internship. But, before that, I needed to gain some knowledge on systematic reviews. And so, I went to a course on the subject.

3.4.2. Articles

As I mentioned previously, all the medical writing work I did was for systematic reviews and meta-analysis in cardiology, under the wing of Dr. Daniel Caldeira. Some of the concepts he was very eager to explore were the safety of the new generation of anticoagulants and the prevalence of anticoagulation in Portugal. In the latter part of the Internship, I started to write a systematic review as a first author, concerning clinical trial monitoring. Not all papers I worked on were published. Two managed to get published, one on the British Medical Journal (BMJ) Heart, and another on the Journal of the Portuguese Society of Cardiology.

The ideas for the systematic reviews came from Dr. Daniel Caldeira's expertise on cardiology subjects. He would write a basic protocol, containing the proposal of the review, and the inclusion and exclusion criteria, and send it to me for evaluation. We would then go back in forth, discussing the concept, and seeing if there was anything that could be improved.

Once the theme of the project was established, we would plan the literature search for the review. Since the papers usually approached complex cardiology subjects, Dr. Daniel would create the search strategy in OVID. I learned to work in OVID and to conduct a systematic search shortly after.

Filtering the articles was a two-person job. I introduced Dr. Daniel Caldeira to the software Endnote, which he started using regularly. Through this software, we could easily manage hundreds of references, and filtering them was much easier. The automatic .pdf search also made this step easier than doing a full manual search.

After the articles were filtered, then came the data collection part. This was usually handled through Excel by me, with the data being then transferred by Dr. Daniel to REFMAN.

When data collection was over and the results were ready to be interpreted, then came the writing part. Before writing a word for the systematic review, I first read all the included articles and made annotations on what I wanted to write about, what I thought was important, and other details. Each draft was sent to Dr. Daniel for evaluation, who would provide guidance and advice through the writing procedure. If he felt I was veering too much from the subject, he would advise me to get back on track, delete all extraneous paragraphs, or even rewrite the entire section. Discussions were particularly hard, was there was lots of evidence sometimes to comb through and analyze.

Once the paper was written, Dr. Daniel would look for a suitable journal to submit the paper. I did not have an opportunity to participate in this section, but I was informed of the discussions that

occurred between Dr. Daniel and the editors of the journal. If an update on the text was needed, we would do the necessary revisions, until we felt the paper meet the feedback of the editor.
I will now provide a brief overview of each paper I worked or helped in some way.

3.4.3. Published Articles

Some of the papers managed to get through the peer review process, and be published in peer-reviewed journals. In those cases, I will provide the abstract of the paper, and a brief description of the journal where it was published.

3.4.3.1. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis

My first major project when I arrived on the LCPT was a systematic review and meta-analysis on the safety of new generation anticoagulants. The project, led by Doutor Daniel Caldeira, sought to evaluate if the new anti-coagulants that are available on the market (Enoxaparin, Eliquis, Dabigatran, and the currently still non-marketed edoxaban) are safe compared to more established therapies such as warfarin.
Most of the large, phase III clinical trials of these drugs were essentially targeted to efficacy endpoints as the primary endpoints, with safety endpoints, such as major bleeding, being secondary endpoints. Since there was no systematic review compiling all the safety data of these drugs, the project was given green light. Moreover, not all created new oral anticoagulants managed to stay in the market. Ximelogatran, a direct factor II inhibitor, was taken from the market after it was shown to increase liver enzymes.
After all major trials of the new drugs were collected information was obtained from the studies. The main data points were major bleeding, clinical relevant bleeding, epistaxis, hemathrosis, intracranial bleeding, and ocular bleeding. Several data points were also obtained for hepatic conditions, and the first article we published with the data concerned the risk of drug-induced liver injury with the new oral anticoagulants. My main contributions were data collection, and writing some paragraphs of text. In the following papers, my writing contributions were more pronounced.
The article, entitled: Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis, was submitted to the journal Heart, a peer reviewed journal for cardiologists, which focuses on showcasing advances in the diagnosis and treatment of cardiovascular diseases (Impact factor - 5.014) by Dr. Daniel Caldeira, the corresponding author.

3.4.3.2. A prevalência da anticoagulação oral em doentes com fibrilhação auricular: revisão sistemática e meta-análise de estudos portugueses

The second paper I worked concerned the prevalence of patients with atrial fibrillation who were anti-coagulated in Portugal. This was an article written in Portuguese, and for the inclusion criteria, we were looking for observational studies conducted in Portugal which reported the prevalence of anti-coagulated patients. Dr. Daniel conducted the initial research, we both filtered the results and evaluated what results fitted the inclusion criteria. Then, we divided the writing tasks. I did writing contributions to every section of the article, save for the statistical portion of the article, which Dr. Daniel handled. This paper was accepted for publication on the Journal of the Portuguese Society of Cardiology, one of the few Portuguese journals indexed in Pubmed, with an impact factor of 0.592.

3.4.4. Unpublished/ work in progress papers

3.4.4.1. Antitrombothics and Vascular dementia

My second systematic review article with Dr. Daniel Caldeira was prevention of dementia by anti-thrombotic medicine. The underlying assumption of the study is to ascertain if antithrombotic agents could reduce the burden and progression of dementia in individuals, since cerebrovascular diseases are a known driver for the development and progression of mild cognitive impairment and vascular dementia. For this, we conducted a database search for articles of randomized clinical trials evaluating the effects of antithrombotic medicine in dementia and that used the Mini Mental Examination Scale (MMSE) to evaluate the effect of these medicines in cognitive function. After reviewing the entire article that we found and excluding any that were not randomized clinical trials or relevant to the subject, data was collected and analysed through REFMAN, a software for conducting meta-analysis.

In this article, I had a very active role in the writing phase of the process. The discussion portion of the article was especially challenging, was I had to take into account all the different bias sources of all analysed clinical trials, and come up with a suitable and reasonable enough explanation of why anti thrombotic did not help at preventing vascular dementia. The discussion also required me to go through the limitations of the MMSE, as this could be a potential source of bias for the results of our study, and addressing the potential bias of the studies that we included in our review.

The paper was, unfortunately, refused for publication on the Heart Journal. We are considering submitting the paper to another journal at the moment, or shelving the idea altogether.

3.4.4.2. Presence of thrombi after three weeks of anti-coagulation therapy

The fourth review article which I worked on sough to evaluate the efficacy of prolonged anticoagulation in patients with atrial fibrillation in solving thrombus, evaluated through transeophageal echocardiography (TEE) before attempting cardioversion. After conducting a database search for articles with the relevant keywords, a total of 283 articles were obtained. An attempt was made to start filtering the articles, but this project was put on standby, since other ideas for papers were deemed more relevant.

3.4.4.3. The impact of acetaminophen in the International Normalized Ratio (INR) of patients treated with vitamin K antagonists: systematic review and meta-analysis.

Another article I worked concerned the impact of acetaminophen in the International Normalized Ratio of patients treated with vitamin K antagonists. Anticoagulants are used to treat or prevent thromboembolic events in multiple conditions (e.g. venous thromboembolism, atrial fibrillation, mechanical heart valves). Vitamin K antagonists are widely prescribed oral anticoagulants, and their efficacy and safety depend on the control of the International Normalized Ratio (INR). Besides the narrow therapeutic window, these drugs have several drug-drug and drug-food interactions. Acetaminophen is a commonly used over-the-counter analgesic, and it is the preferred drug for anti-coagulated patients, as non-steroidal anti-inflammatory drugs carry a significant risk of bleeding due to increases of INR and direct gastrointestinal effects. Observational data have suggested that acetaminophen in moderate doses was associated to increased INR values and bleeding events (37, 38).

All the reviews that addressed the topic were in favor of the existence of a potential interaction between acetaminophen and vitamin K antagonists. However, Dr. Daniel knew that the dimension of the effect remained to be determined, and thus, we decided to review all data from randomized controlled trials to estimate the impact of acetaminophen in the INR of patients treated with VKA. In this paper my contributions were solely concerned with data collection and writing. Dr. Daniel Is currently preparing for submission of the paper.

3.4.4.4. Clinical trial monitoring – where do we stand? A systematic review

This paper was prompted by a challenge of Professor Joaquim Ferreira, who asked me and my trainee colleagues to write a paper on a matter related to clinical trials. I choose to write a systematic review concerning clinical trial monitoring, more specifically, the ongoing debate of on-site monitoring versus the newer concept of centralized monitoring, and search the literature for where is the scientific community leaning more towards. On-site monitoring is where the clinical

research associate, or monitor, is assigned to monitor a clinical or observational trial in a study centre or group of study centres, and then carries an in-person evaluation at the sites. Centralized monitoring is more technology reliant, where the clinical research associate, or any assigned sponsor personnel, conducts a remote evaluation of the study centre. Centralized monitoring was made possible by the evolution of modern information technologies, and the advent of electronic data capture, most noticeably the eCRF.

All the knowledge I gathered from my previous projects with Dr. Daniel were put to the test in this paper. I had to write a protocol for the review, write down the inclusion and exclusion criteria, delineate the search strategy that I was going to use, filter the results, and read and summarize all included articles into a concise summary reflecting the current reality of clinical trial monitoring. The article is currently in pre-submission, as I am still deciding on one of two possible journals to send the paper.

3.5. Other projects

Alongside the clinical trial monitoring activities I held on the NCRU, and the medical writing projects I was able to participate in the LCPT, I also participated in a variety of assorted projects throughout the internship. These activities were very enriching on a formative level, and were additional sources of training, education, and experience. These included:

- A clinical trial audit from a sponsor to the NCRU;
- A monitoring visit for the Registry study, in which me, Dra. Maria Finisterra and my internship colleagues conducted a monitoring visit to the Hospital Professor Doutor Fernando Fonseca, EPE;
- A week at the Pharmacovigilance Unit of Lisboa and Vale do Tejo;
- Standard Operating Procedures (SOPs) for various procedures of the NCRU;
- Work on a proposal for a research grant;
- Assorted meetings;
- A course on GCPs, another on systematic reviews (already discussed on this report) and an intensive, 1 week course on pharmacovigilance.

The following paragraphs will discuss in detail each of these projects.

3.5.1. Audit

From April 28th to April 30th, the NCRU had an audit from a sponsor, who sent a monitor of their own to check if the trial was being properly conducted at the centre, and everything was protocol compliant. This was a challenge to me and our team, who had an intense preparation phase ahead

of the audit, to ensure that everything was in place for the audit. Throughout the entire audit, most of the research team was available to the auditor, to answer possible questions.
During the closing meeting, the auditor presented the most relevant findings, which were discussed with the principal investigator and the other team members.

3.5.2. REGISTRY monitoring visit

In the Internship, I was also involved, to a minor degree, in a prospective cohort study of the European Huntington's Disease Network, the REGISTRY study. The registry study is the biggest project of the CHDI. REGISTRY is a multi-centre, multi-national observational study, which aims to follow a large cohort of Huntington's disease patients and controls, to further characterize the disease, among other things. It is a part of the Huntington Project, a worldwide collaboration dedicated to finding treatments for Huntington's disease. REGISTRY is sponsored by the High Q Foundation, a non-profit organisation that supports a variety of research projects seeking to find treatments for HD(39). This study is currently in its third iteration, and a fourth iteration, entitled Enroll-HD, is scheduled to begin soon(40).
The CHLN, E.P.E. – HSM is the Portuguese language coordinator, meaning that it is responsible for coordinating and monitoring all centres that participate in the study in Portugal. It managed to participate in a monitoring visit to the Hospital Professor Hospital Professor Doutor Fernando Fonseca, EPE, alongside my Dr. Maria Finisterra and my colleagues.
Performing a co-monitoring visit of the Registry study was a very interesting task, since it gave me the chance to interact with other investigators, practice source data verification, and conduct basic quality assurance procedures of the data. Our main goal on the monitoring visit was to check if the protocol was being followed and the rights, safety and well-being of patient's was being protected, and that all data was being collected correctly. This activity showed me that different sites have different ways of organizing themselves.

3.5.3. Journal Club

Every Wednesday, the investigation team members of the NCRU and of the clinical pharmacology unit gathered at 8 am to attend the clinical research centre's Journal Club. Each week, one member of the team was assigned to bring a recent article in the field of neurology and neurosciences, and he/ she had to explain it and showcase the study's findings to the rest of the team. A short discussion usually ensued, ranging from considerations on the design of the study, the potential therapeutic applications of the findings, amongst other relevant topics. These discussions were particularly enlightening, as they showcased the group's dynamic and different backgrounds, and

what prospects these studies could bring to the activities of a research centre. These morning sessions also served a double purpose, as they allowed for the team to meet and share information, provide important heads-up and face to face time and to ensure that not all conversations among team members were done through e-mails.

3.5.4. Wednesday afternoon meetings

Every Wednesday afternoon, a meeting was held on the Clinical Pharmacology Laboratory with all members of the team. In these meetings, a different team member came forth with a presentation concerning a project that they were working on. This helped the team members get to know what everyone is working on, discuss the project or idea of a project, provide feedback and opinions, or just show the results of their labour. The first of such meetings was on November 13th, where everyone got together on the Clinical Pharmacology Laboratory, introduced themselves and shared their ongoing projects. The following weeks, the meetings started to be led by a different member each week, and their projects were showcased to everyone.

3.5.5. Candidatura MANTERO BELARDO Santa Casa Da Misericordia

In my second week of the internship, I was transferred to the Clinical Pharmacology laboratory. Immediately after joining the laboratory, I collaborated on the submission of a project to a research grant sponsored by the Santa Casa da Misericórdia de Lisboa, the Manterdo Belardo Research Grant, for the treatment of aging related diseases, such as Parkinson's and Alzheimer's disease. The Santa Casa da Misericórdia de Lisboa also had another research grant, the Melo e Castro Award for the recovery and treatment of vertebro-medullary injuries.

This was the largest grant given to medical and scientific research in neuroscience ever made in Portugal, awarding two research projects 200,000 euros each. The jury was comprised of the scientist Alexandre Quintanilla Paul Correia de Sá, University of Porto, Catarina Resende de Oliveira, University of Coimbra, Jorge Laíns, from the Portuguese Society of Physical and Rehabilitation Medicine, Jose Pimentel, from the Portuguese Society of Neurology, Rui Costa of the Portuguese Society for Neuroscience, and George Perry, a world expert on Alzheimer's disease from the College of Sciences, University of Texas. The initiative also had the backing of the neurologist António Damásio.

The project, entitled **HelPD - LATE-STAGE PARKINSON'S DISEASE AS A MODEL FOR ASSESSING AND MANAGING ELDERLY PEOPLE WITH MULTIPLE PPHYSICAL, MENTAL AND SOCIAL DISABILITIES** - was divided in eight different sub projects, dubbed Working packages. The project's overall goal was to

further the understanding of Late-Stage Parkinson's disease patients, a stage of the disease where much information is still lacking. The observational studies include an evaluation of clinical manifestations, functional disability and quality of life, disease prognosis, the benefits from pharmacological and non-pharmacological interventions, the needs and provision of care, and the burdens of the caregivers that handle this disease. This project also included an assessment on the frequency of parkinsonism and PD in the elderly population living in nursing homes of the Santa Casa da Misericórdia de Lisboa.

The experience was quite fruitful, and a very good learning experience. It allowed me to understand the relationship between the management division and the research unit, grasp some basic concepts on budget allocation and provide some written content for the submission, including the abstract, in two languages. I was also responsible for the creation of the logo for the project (**Figure 3**).

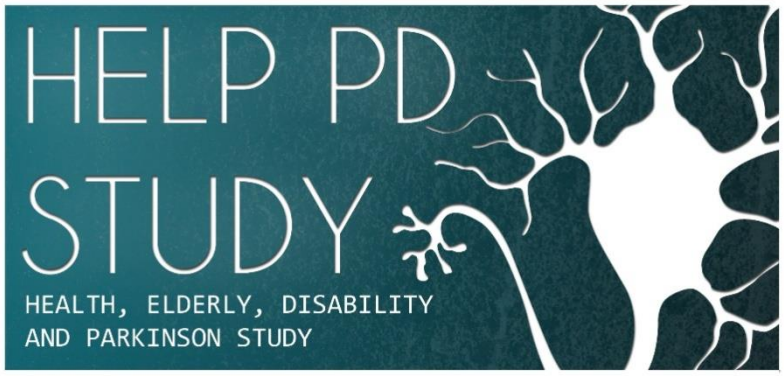

Figure 3 - Logo of the project, created with Photoshop CS4

The research grant had a total of more than 70 submissions from research groups around the country. The winner was revealed on December 5th, at 6 p.m at the Meo Arena in Lisbon. The awards were presented by João Lobo Antunes, president of the jury. The Prime Minister, Pedro Passos Coelho, and Santa Casa da Misericordia de Lisboa provider, Pedro Santana Lopes, also participated in the event.

The two winners were chosen from among 79 projects that have entered the contest, involving a total of 289 researchers, with contributions from 12 countries(41).

Unfortunately, our project did not won the main prize. The networks that were established, however, will hopefully be fostered for future projects.

3.5.6. Standard operating procedures – SOPS

SOPs are documents which provide written instructions on how to conduct a given procedure, to ensure that it is conducted in uniformity by all members of an organization(7). These documents provide guidance to workers at an organization, to ensure that all processes are standardized. SOPs are of the foundations of a quality system, and they are a part of the Quality Management System (QMS) requirements concerning documentation, as stated in ISO 9001: 2008 A quality system is fundamental for the proper management of an organization(42).

While I stopped working directly with the NCRU in my second week of the internship until November, I was still interested in providing support work in any way I could to the team over at the Neurology clinical research centre. When Dr Ana Noronha asked me if I could provide assistance in writing and reviewing Standard Operating Procedures for the centre, I immediately jumped at the opportunity.

The SOPs that existed mainly described the procedures of the centre, from handling source documents to patient recruitment. Before I even started reviewing the existing ones, I thought it would be to the site's best interests to have a SOP on how one should create SOP's for the research centre. This helped harmonize the creation procedure of SOPs in the research centre, and it was warmly received by my colleagues.

Before beginning writing the SOPs, I made sure that I was familiar with the site procedures that were the focus of the SOPs. Any doubts that I had concerning a procedure, I made sure to ask Dr. Ana Noronha or Dr. Maria Finisterra. This ensured that the procedure that was written on the SOP was faithful to what happened at the NCRU.

Alongside the SOP for creating SOPs, a total of 22 Sops were either reviewed, or created. Some SOPs that were reviewed underwent lengthy changes. The original SOPs were created by my fellow Master's colleague Rita Carreiro, and her work was excellent from the get go. All the changes I did were done as to better reflect the current procedures in place at the centre, and the new SOPs that were created were to done to fill some gaps perceived by the team.

I continued working on the SOPS when I returned to the Clinical research centre, creating new ones after a meeting with Dr. Ana Noronha and Dr. Ricardo. All SOPs define responsibilities for all members of the study site team in the NCRU, and provide ample instructions on how to perform a given procedure. The work that was initially created by Rita Carreiro was a solid foundation for which to work upon, and improve in some ways I felt were important. While they are still being reviewed for implementation, I hope that they are of use to the NCRU in the future.

3.5.7. Pharmacovigilance – Unidade de Farmacovigilância de Lisboa e Vale do Tejo

Pharmacovigilance is a safety concerned activity that aims to improve the quality and the safety of medicines, in defense of the user and the public health, through the evaluation and prevention of adverse drug events of drugs. The Unidade de Farmacovigilancia de Lisboa e Vale do Tejo is one of the parts of the National Pharmacovigilance system, and thus it shares with the SNF the goal to improve the safety of the patients taking medicines.

In the internship, I had the opportunity to see for a week, from October 28th 2014 to November 1th, how was a pharmacovigilance unit organized, and I was really surprised with it. It essentially ran like a clockwork machine. Every person was responsible for a distinct set of tasks, in sequence, with the workflow resembling an assembly line. First, the adverse drug reaction notification was received. A time limit was set on the calendar for completing the coding, recording the adverse event, and conducting the follow up process. During the week, I managed to code a few adverse drug reactions by myself, under the close supervision of Dr. Ana Marta. I also did the follow up process of one serious adverse drug reaction, and managed to get an inside look how the unit dealt with more complicated reactions.

While it was very short, it was also very fascinating to observe and play a small part in such a well-organized unit, where everything ran in sequence. I am very grateful to the members of the pharmacovigilance unit, for allowing me to observe and participate in pharmacovigilance procedures.

3.6. Courses

During the internship, I had often times the opportunity to attend some additional courses. These provided me with extra training and knowledge that were quite useful during the internship. I received three additional courses, one concerning systematic reviews and meta-analysis, another on Good Clinical Practices, and the last one was an intensive course on pharmacovigilance.

3.6.1. Systematic reviews and meta-analysis course

In my second week of the internship, from September 11 to September 12, I attended the sSystematic reviews and meta-analysis workshop presided by Dr. Daniel Caldeira, a cardiologist, at the hospital Santa Maria. Since some of my work during the internship was going to be focused on systematic reviews and meta-analysis, I had interest in watching the course, and was fortunate to be invited by Dr. Daniel to watch the presentation.

The course was a very enriching experience, and showed me the different steps one was to consider when planning a systematic review. The PICOS (short for participants, interventions, comparators, outcomes, and study design) methodology was introduced, alongside essential tips on managing the

scope of the project, minding the article reviewer, analysis of forest plots and pooling results from various clinical trials/ studies to come with a conclusion regarding a therapy/ intervention. The workshop also focused special attention on scientific databases, and students were asked to share their experiences when working with databases such as PUBMED and ISI. Search strategies were also shown for when conducting an exhaustive search on PUBMED.

After the course was over, I gained a very solid base to start building upon my knowledge of systematic reviews and meta-analysis. During the internship, I sought out additional resources to help me understand better the process behind a systematic research. One of the skills I learned was how to perform a systematic search on the OVID database, a skill which helped me greatly in one of my papers.

3.6.2. GCP course

On October 1st, 2013, I attended the GCP workshop, headed by Doc Ingrid Klinman, of the Pharmatrain Initative, under the inauguration activities of the 2013/2014 lective year of the Training Programme in Pharmaceutical Medicine.

GCP were given an historical background, from the document that started with all, the Nuremberg Code, to the different versions of the Helsinki Declaration that have appeared through the years. The GCP principles were detailed by the speaker, with dilemmas like patient compliance, informed consent from minors and the different interpretations of the GCP under the clinical trial directive of each country being also discussed.

This workshop was particularly interesting in its second half, as various examples and ethical dilemmas were presented, and we were requested to give our opinion on them.

This course was an excellent supplement to the knowledge obtained in the bachelor and master's degree. It allowed me to tackle with more confidence the clinical trial coordination activities of the NCRU.

3.6.3. Pharmacovigilance course

From October 21 to October 24, I attended an intensive course on pharmacovigilance on the hospital of Santa Maria/ Edificio Egas Moniz. The course provided an overview on the different reporting mechanisms of drug adverse reactions, the ins and outs of the risk benefit evaluation, pharmaco epidemiology studies and causality assessment of adverse reactions. The course also provided an overview of the national pharmacovigilance system and its story and on the pharmacovigilance

systems employed in other countries. The course then gave a rundown of the adverse events are most common for the different anatomical main groups.

4. Discussion

Clinical trials are the current gold standard for obtaining evidence concerning a new pharmaceutical, as they offer a true and tested method of obtaining evidence on its safety and efficacy. I developed my training in a clinical research site that conducts clinical trials and observational studies to help further scientific progress and contribute to patients' healthcare and quality of life.

While I believe that this report is a very thorough document, describing all the major projects and activities I was in, it does not demonstrate all the effort that I poured during these 10 months, since so many little things happened. The experiences, knowledge, and hard work made this internship a deeply enriching year. I want to thank everyone at the research team that accompanied me during these 10 months, for their patient, wisdom, and feedback that they provided.

As we saw in the introduction and Chapter 2, clinical trials are extremely demanding for any professional who works on them. They require the individual to be organized, to pay careful attention to the protocol, and have an eye for details. Communication skills are a must, and a professional must know to adapt his language as needed, and always in a scientifically correct manner. As a clinical trial coordinator trainee, this internship allowed me to improve tremendously my organization skills. Making sure that everything was well organized, in a coherent manner, properly signed and dated, and that the trials kept flowing in a good pace, were some of the tasks that allowed me to hone my organization skills. Scheduling appointments, preparing visits, checking the protocol and making sure that nothing was missed made me focus more on the details, without losing sight of the big picture. There is a big pressure in clinical trials in ensuring that nothing goes wrong, and that protocol deviations are avoided at all costs. Missing a procedure that collects information might seem like a minor deviation, but others, like a patient taking prohibited medication, are more serious.

This point highlights the most important aspect of clinical trial conduction – making sure that all trials are conducted ethically as defined by the International Conference on Harmonization Guidelines (ICH), especially the E6, concerning Good Clinical Practices. The entire team that is working on a clinical trial has a moral and ethical responsibility to the patient, and the wellbeing of any participant is the most important factor in a clinical trial.

Many guidance and ethics documents were discussed in great detail throughout my classes in the bachelor and the masters, including the Helsinki Declaration, the ICH-GCPs, Directive 2001/20/CE, Directive 2005/28/CE, and many others. Having a chance to apply the knowledge gained in the last four years in a real-world context was one of the main motivations for choosing to do an internship at a clinical research site, and one such as the NCRU was the perfect place.

This NCRU is extremely concerned with recruitment of patients, and it comes as no surprise that it has a high rate of recruitment and retention in clinical trials when compared to other Portuguese sites for the same clinical trials, and a low rate of dropouts. Being able to learn and work in such a tightly structured organization was an opportunity like few others.

The diverse range of professionals that I have met during the internship greatly improved my communication skills and my knowledge. From neurologists, psychologists, other coordinators, monitors and statisticians, the broad range of healthcare professionals, who were always eager to share their experience in the clinical trial field, helped me deepen my knowledge on this field.

The bachelor's and master's degree provided me with a solid background to work in an environment such as this. Adaptation was also very fast, and while learning was a constant experience, in very little time I managed to become a productive member of the team. The initial instructions were very important to learn the workflow of the centre, and how things were done, and some practical things that were not taught during my bachelor's and master's degree. Processing biological samples was one such thing. I practiced it, and learned to pay very close attention when handling samples from different patients, as to not mix samples. Performing ECGs and measuring vital signs were also activities completely unknown for me. While I had few opportunities to do ECGs since I was somewhat slow when placing the electrodes, I did manage to become efficient at measuring the vital signs of a patient.

While the training I received was mostly during the beginning of the internship, it should be mentioned that the entire internship was a learning experience, where the knowledge obtained from the Master's was constantly refined and improved. Moreover, due to the number of trials, it was not uncommon during the internship to look at a week's agenda, and see each day filled with appointments of patients, each from different trials. The sheer diversity of trials meant a wide range of procedures to keep track of. Add up the fact that different visits from the same trial might have different procedures, and you find yourself with a lot of information to manage. Teamwork was thus very important. Different coordinators could "specialize" in some trials, while providing backup for the remaining trials. Checking the protocols regularly was also essential.

The inclusion of the first patient in the EXPAND study was a milestone I am proud of, and It made me feel like my contributions were important and that the team worked together very well. In what is a complex trial, the entire team went over in detail every procedure and the appropriate timings, making sure that nothing went wrong. Patient recruitment was a very enthusiastic experience that I could experience. Usually, patients were very eager to participate in a clinical trial or observational study, and contribute to the advance of medicine and hopefully improve their quality of life. Even

more rewarding was seeing improvements in some patients every time they came to the site. In these occasions, I could not help to feel very joyful and accomplished.

But my experience with clinical trials was not solely on the EXPAND trial. During the Internship, there were more than 30 clinical or observational studies occurring, so I had ample experience with a lot of clinical trials. Lots of protocols with different levels of complexity, study designs and procedures, from a range of different sponsors and in different pathologies passed through my hands. I learned tremendously from reading these documents, and applying the procedures they described. The contact with different diseases consolidated my background knowledge of the each different pathology, alongside the current available treatments. I became very proficient in understanding the trial and all its procedures, and a lot of times my feedback was asked by other members of the team.

Many trials were reliant on information technology innovations, with iPADs, digital pens, mobile telemetry devices and laptops being a common sight when coordinating trials. This surge of new technologies made some of the newer trials being really fascinating projects, and while not everything was perfect technology wise, it was very exciting whenever a new equipment arrived on the mail. As for eCRFs, I became quite capable of handling different eCRF technologies, and how they worked was pretty intuitive to me.

The audit we received was very important to my growth as a professional of clinical research. Audits are an opportunity for improve the gaps and flaws that the research site might have, and to check if everyone who plays a role in the trial are on the same page concerning the procedures.

Overall, I would say that I was very fortunate in having my internship in the NCRU, as it allowed me to fulfill all my objectives for the internship. I managed to witness and play an active role in a clinical trial, learn skills related to the coordination and management of a clinical trial (in essence, learn the trade), and apply the knowledge I gained on both my bachelor's and my master's in the coordination of a clinical trial centre.

As for medical writing, I have to say it was a very rewarding experience. I really enjoy writing, and being able to participate in research projects as a writer was a great opportunity. Like in clinical trial coordination, my skillset increased tremendously from playing an active role in these projects. Each new project provided me with knowledge on an array of cardiology subjects. I had to study each topic carefully, as to be able to write on a given subject with confidence.

My writing skills also improved. I learned the value of short, to the point sentences in a complex scientific document. Trying to distance myself from the text, and read it see if it engaged me was an interesting experiment.

I learned how to search on OVID, and to construct a systematic search strategy. This is a very useful skill to have, and one I hope to have lots of chances to apply in the future.

While my statistic skills improved little, seeing as I did not do anything related to statistics save for the data collection, I managed to grasp some basic concepts on how a meta-analysis was conducted, the type of software that was used, and how to interpret the final result, a forest plot.

The medical writing activities I engaged in also provided me with a unique opportunity to publish a paper in a peer reviewed journal. At first, I struggled a bit the repetitiveness of data collection, but through sheer repetition I managed to become good in locating the data that I needed and transferring it to a database. I really enjoyed writing for the papers, and these projects were a great accomplishment for me and a great source of joy. Being able to see my name in PubMed as a second author of two articles, alongside with all the experience I gained, made the internship one of the most enriching experiences for me ever.

The development of SOPs allowed me to apply my writing skills and knowledge on quality to hopefully improve the site's procedures, and build upon the already existing SOPs. Now, every time a new member is recruited to the staff, there are SOPs to train this new collaborator in the site procedures, and help them easily adapt to the site's daily routine.

5. Conclusion

Working in clinical research coordination was a tremendous growth experience for me. The work that we did while I was a trainee at the NCRU was very focused on the patient. Every day, we did do our best to give the opportunity for a patient to receive innovative treatments and improve their quality of life. Each patient appointment, we hoped that our work was helping science progress, so that one day, hopefully, terrible chronic diseases like Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Huntington's disease, and many others, will have a cure.

The internship allowed me to participate in different projects within two different units, giving me a wide range of learning opportunities, with each day bringing a new challenge. While the majority of the internship concerned clinical trial coordination, I had a wide avenue of other projects to participate on. Medical writing, pharmacovigilance, quality systems, the list goes on and on.

It is worth noting that, through the skills I gained at the bachelors and masters, I managed to provide something of value to the hosting institution, making this internship a mutual gaining experience. It was a way to put into practice what I had learnt at the University and was a bridge between the academic and real world. There were many occasions where I provided valuable input to an occurrence, where I showed knowledge and understanding of the study's protocols.

The study coordinator is truly an essential individual to ensure that the trial goes well. It is hard to imagine a clinical trial being run without a study coordinator behind it, making sure that the entire team is on the same page.

A study coordinator must always keep in mind the patient's safety, the ICH GCPs and overarching ethical principles, and must always be concerned with protocol compliance as he/she organises the study procedure. By acting as the bridge between the research staff and the sponsor/clinical research organization, this professional allows both entities to provide feedback on each other's activities.

I enjoyed very much to interact with the patients during the internship. Each person had a different story to tell. Sometimes, it was hard interacting with a patient who was a bit more impolite, but in these (rare) cases, I had to imagine myself in their shoes, and what I would be thinking if I carried the terrible burden that most of the patients at the NCRU carry. Most of the patients were very nice, and observing the positive progression that some patients was extremely satisfying. In a very small way, I helped the patient improve his quality of life, or lessen a symptom that really incapacitated the patient. Moments similar like these were highlights of the internship.

While I greatly enjoyed my time as a study coordinator, I must say that writing was where I really felt that I was good at. It's an activity that feels very easy for me, as it just comes naturally in a way. I would like in the future, to go a bit more deep into medical writing, just to see if it really fits me

when done for a longer period of time, say, a year. That is not to say that I did not enjoy clinical trial coordination, far from it. These months as a clinical trial coordinator left many good memories, and the entire experience was life changing. If I attempt to move to medical writing, it will be more to satisfy my curiosity, and see what comes out of it.

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