Universidade de Aveiro Departamento de Ciências Médicas
2016

RAQUEL FILIPA DE OLIVEIRA RODRIGUES

Relatório de Estágio Curricular numa Unidade de Investigação Clínica

Report of a Curricular Training in a Clinical Research Unit

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Auxiliar da Faculdade de Medicina da Universidade de Lisboa e da Professora Doutora Maria Joana da Costa Gomes da Silva, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este trabalho aos meus pais, que nunca mediram esforços para me tornarem uma pessoa mais feliz.

Ao meu avô, que sei que sentiria um enorme orgulho em mim.

o júri

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agradecimentos

É com especial carinho que agradeço a todos aqueles que tornaram este estágio possível e que contribuíram de alguma forma na minha formação profissional e crescimento pessoal.

Ao Professor Doutor Joaquim Ferreira, pela oportunidade de integrar a sua equipa de trabalho, pela orientação e conhecimentos transmitidos durante o estágio.

Ao Professor Doutor Luís Almeida e ao Professor Doutor Bruno Gago, pela oportunidade de participar no Mestrado em Biomedicina Farmacêutica e pela constante partilha de conhecimentos e experiências.

À Professora Doutora Joana Silva, coorientadora deste estágio, pelos conselhos e orientação na revisão crítica deste relatório, e por toda a disponibilidade demonstrada.

A toda a equipa do Laboratório de Farmacologia Clínica, em especial ao Dr. Daniel Caldeira e ao Professor Doutor Ricardo Fernandes, por terem acreditado que o meu contributo seria uma mais-valia nos seus projetos e por tudo o que me ensinaram. À Dr.ª Ana Marta Anes e à Dr.ª Ana Noronha, por tão bem me terem acolhido nos seus grupos de trabalho e pelo apoio e partilha constantes. Um agradecimento ao Márcio Barra, à Ana Augusto e à Ana Salgueiro, pela paciência e por estarem sempre disponíveis para ajudar.

À Eunice, ao João, à Nádia e ao Nuno, pela amizade e partilha de experiências durante este período de estágio.

Á a toda a minha família, em especial aos meus pais, por tornarem possível a conclusão de mais uma etapa da minha vida. Obrigada pelo amor, apoio incondicional e carinho que sempre me deram. Ao meu irmão, pela alegria e força em todos os momentos. Á Vera, pela paciência e amizade.

Á Patrícia e à Rita, por serem as amigas que qualquer pessoa desejaria ter, pela compreensão e apoio incondicional.

À Cátia, à Diana, à Jéssica, à Cindy, à Isabela e à Sandrine. Porque mesmo longe, nunca desistimos daquilo que nos une. Às minhas amigas de sempre: Cátia e Ana, pelo carinho e por sempre terem acreditado em mim.

Aos meus tios Francelina e José e aos meus primos Xana e João, por me terem acolhido e ajudado durante estes dois anos em Lisboa.

Aos meus colegas da Licenciatura e do Mestrado, por todos os momentos felizes partilhados.

palavras-chave

Biomedicina Farmacêutica; Farmacologia Clínica; Ensaios Clínicos; Estudos Observacionais; Investigação Clínica; Escrita Cientifica; Farmacovigilância; Monitorização; Coordenação de Ensaios Clínicos

resumo

Este relatório apresenta as atividades e projetos desenvolvidos durante o estágio curricular numa unidade de investigação clínica, o Laboratório de Farmacologia Clínica, parte do Instituto de Medicina Molecular.
O estágio teve a duração de 10 meses, sendo que a atividade mais relevante foi a coordenação de ensaios clínicos na área de neurologia. Também colaborei em atividades de escrita científica, nomeadamente revisões sistemáticas em cardiologia, pediatria e farmacologia clínica. Tive ainda a oportunidade de participar na gestão de bases de dados clínicos, na monitorização e coordenação de estudos observacionais e em atividades de farmacovigilância.
Refere-se, no estado da arte, o processo de Investigação e Desenvolvimento de novos medicamentos e são caracterizados alguns aspetos da investigação clínica em Portugal, nomeadamente o enquadramento da atividade, com enfoque na Neurologia. É ainda contextualizada a Farmacovigilância no atual sistema de avaliação da segurança dos medicamentos em Portugal.
Este período de estágio possibilitou colocar em prática os conhecimentos que adquiri na Universidade, mas também expandi-los. Ao longo deste estágio, pude observar de perto dificuldades logísticas com que um centro de investigação se depara durante a condução de ensaios clínicos. Aprofundei também o conhecimento em investigação clínica, enquanto expandi as minhas áreas de interesse profissional. Pude melhorar as minhas capacidades de redação de documentos científicos, através da elaboração de várias revisões sistemáticas e meta-análises. Percebi também a importância das unidades de investigação clínica, bem como o papel fundamental dos coordenadores de ensaios clínicos na rigorosa execução de todos os procedimentos dos estudos e na comunicação entre os elementos da equipa. O treino específico centrou-se em estudos clínicos, nomeadamente ensaios clínicos de fase II e III, e estudos observacionais em doenças neurodegenerativas. Apoiei a coordenação de quatro estudos em Polineuropatia Amiloidótica Familiar, dois em doença de Huntington, dois em doença de Parkinson, um em doença de Alzheimer e um em Distonia Cervical Idiopática. O contacto com os doentes foi parte muito importante da experiência em coordenação de ensaios clínicos.
Considero que este estágio curricular foi uma experiência muito enriquecedora, onde comecei a executar atividades de investigação clínica. Desta forma, termino o estágio com motivação e interesse em trabalhar na área de coordenação de ensaios clínicos e gestão de projeto.

keywords

Pharmaceutical Biomedicine; Clinical Pharmacology; Clinical Trials; Observational Studies; Clinical Research; Medical Writing; Pharmacovigilance; Monitoring; Clinical Trials Coordination

abstract

This report presents the activities and projects developed during the curricular internship in a clinical research unit, the Laboratory of Clinical Pharmacology, part of the Institute of Molecular Medicine.

The internship had a duration of 10 months, being that the most relevant activity was the coordination of clinical trials in the area of neurology. I also collaborated in medical writing activities, namely systematic reviews on cardiology, paediatrics and clinical pharmacology. I had also the opportunity to participate in the management of clinical databases, in the monitoring and coordination of observational studies and in pharmacovigilance activities.

In the State-of-the-Art section is referred the process of Research and Development of new drugs and are characterized some aspects of clinical research in Portugal, namely the framework of the activity, with a focus in Neurology. Furthermore, the current context of Pharmacovigilance in the system of drug safety evaluation, in Portugal, is presented.

This training period enabled me not only to put into practice the knowledge acquired at the University, but also expanding it. During this internship, I could closely observe the logistical difficulties that a research centre faces during the conduction of clinical trials. I also increased my knowledge in clinical research while expanding my areas of professional interest. I could improve my writing skills of scientific documents, through the elaboration of several systematic reviews and meta-analysis. I also realized the importance of clinical research units as well as the crucial role of clinical trial coordinators in the rigorous implementation of all the studies' procedures and in the communication between team members. This specific training focused on clinical studies, namely phases II and III clinical trials and observational studies in neurodegenerative diseases. I supported the coordination of four studies in Familial Amyloidotic Polyneuropathy, two in Huntington's disease, two in Parkinson's disease, one in Alzheimer's disease and one in Idiopathic Cervical Dystonia. The contact with patients was a very important part of my experience in clinical trials coordination.

I consider that this internship was a very enriching experience, where I started to perform clinical research activities. Thus, I finish the internship with motivation and interest to work in the area of clinical trials coordination and project management.

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Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
CEIC	Comissão de Ética para a Investigação Clínica
CIC-CAML	Centro de Investigação Clínica do Centro Académico de Medicina de Lisboa
CNPD	Comissão Nacional de Proteção de Dados
CRA	Clinical Research Associate
CRF	Case Report Form
eCRF	electronic Case Report Form
CRO	Clinical Research Organization
EMA	European Medicines Agency
EU	European Union
FAP	Familial Amyloidotic Polyneuropathy
FMUL	Faculty of Medicine of University of Lisbon
GCP	Good Clinical Practices
HSM-CHLN	Hospital de Santa Maria – Centro Hospitalar Lisboa Norte
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMM	Institute of Molecular Medicine
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
ISO	International Organization for Standardization
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LCP	Laboratory of Clinical Pharmacology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NOAC	New Oral Anticoagulant
PI	Principal Investigator
QMS	Quality Management System
RCT	Randomized Controlled Trial

R&D	Research and Development
RevMan	Review Manager
SAE	Serious Adverse Event
UFLVT	Unidade de Farmacovigilância de Lisboa e Vale do Tejo
USA	United States of America
WHO	World Health Organization

1. Introduction

During the second year of my Master's degree in Pharmaceutical Medicine at the University of Aveiro, which is affiliated to the PharmaTrain programme, I had the opportunity to carry out a curricular internship at the Laboratory of Clinical Pharmacology (LCP). LCP is an organic unit that belongs to the Institute of Molecular Medicine (IMM) and has its facilities in the Faculty of Medicine of the University of Lisbon (FMUL).

This curricular internship lasted for about ten months, during which time I acquired knowledge and experience in four different sub-units – the Biostatistics and Methodological sub-unit; the Outcomes sub-unit; the Safety and Drug Utilization Research sub-unit and the Clinical Trials sub-unit, which is focused mainly on neurodegenerative disorders.

My training report, organized in five chapters, is the compilation of all the activities performed in the LCP and its functional sub-units. The first chapter is an introduction to contextualise the training and to present how it was structured. This introduction includes a characterisation of the host institution, the objectives defined for my internship and a description of the state-of-the-art on clinical research and clinical trials, namely their current regulatory and scientific framework in Portugal, as well as a reference to the pharmaceutical Research and Development (R&D) process.

In the second chapter – "On the job training"- I described the activities and projects that I had the opportunity to develop during my internship and which enabled me to gain experience in various aspects of clinical research. I divided this chapter in two subchapters: specific training and generic training. Specific training comprises the activities of clinical studies' coordination that I performed in LCP. Generic training corresponds to the data management, medical writing and Pharmacovigilance activities, as well as the training sessions, workshops and training courses performed during the internship.

The third section, Discussion, presents the knowledge and lessons learnt during the training and if I achieved the proposed training objectives. The fourth chapter corresponds to the Conclusion, where I provide feedback about my experience, performance during the ten months of training, what it brought to my education, the positive aspects and what I would like to improve in the future.

1.1 Vision of the Host Institution

My curricular internship was performed at the LCP, which belongs to IMM. LCP has functional sub-units: the Clinical Trials sub-unit of the Neurology Department from Hospital de Santa Maria - Centro Hospitalar Lisboa Norte (HSM-CHLN); Drug Evaluation and Systematic Reviews sub-unit, that corresponds to the Movement Disorders Cochrane Collaboration Review Group; the Safety and Drug Utilization Research sub-unit, where the Unidade de Farmacovigilância de Lisboa e Vale do Tejo (UFLVT) is located; the Outcomes sub-unit; the Biostatistics and Methodological sub-unit and the Pharmaco Magnetic Resonance Imaging (MRI) sub-unit (1, 2).

IMM is an associate laboratory recognized for the biomedical research conducted there. Furthermore, IMM has established collaborative projects with HSM-CHLN and with several prestigious international institutions (3).

This institution is located in the campus of FMUL and HSM-CHLN (3). IMM, FMUL and HSM-CHLN have recently formed the Centro Académico de Medicina de Lisboa, a consortium that is aiming to promote the academic dimension and edification in clinical practice, the modernization and development of research, medical education and innovation of health sciences. This aggregation renews the concept of teaching hospital and means to secure the essential compatibility of medical education with research and patient care, allowing the creation of start-up companies and multiple research collaborations (4).

IMM is composed of several laboratories where researchers develop their projects. One of these units is the LCP, where I performed my curricular internship (3).

1.1.1. Laboratory of Clinical Pharmacology

Although LCP belongs to IMM, its facilities are located at FMUL and at the HSM-CHLN. HSM-CHLN is the largest hospital in Portugal, with several medical specialities and specialized services (5). In 2008, the fusion of HSM and Hospital Pulido Valente constituted the CHLN, a highly differentiated and distinguished institution, embedded in the Região de Saúde de Lisboa e Vale do Tejo. CHLN is responsible for the direct provision of health care to 373 000 inhabitants. In addition to providing health services to the people living in Lisbon, these two hospitals also receive patients from all parts of Portugal and from abroad (5).

The research team from the Neuropharmacology Unit of the Neurology Clinical Research Unit and the members of the Laboratory of Clinical Pharmacology and Therapeutics created LCP on July 2013 (6). Professor Joaquim Ferreira is now head of this laboratory.

The functional sub-units of LCP are represented in Figure 1. During its first year, the research team grew mainly with the arrival of new MSc and PhD students. The Drug Evaluation and Systematic Reviews sub-unit (Movement Disorders Cochrane Collaboration Review Group) was consolidated and the Safety and Drug Utilization Research Unit (UFVLT) gained sustainability with a revised service contract established with the National Authority of Medicines and Health Products - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED). After, a Biostatistics and Methodological sub-unit was developed and, more recently, a Pharmaco MRI sub-unit was created (Figure 1) (7).

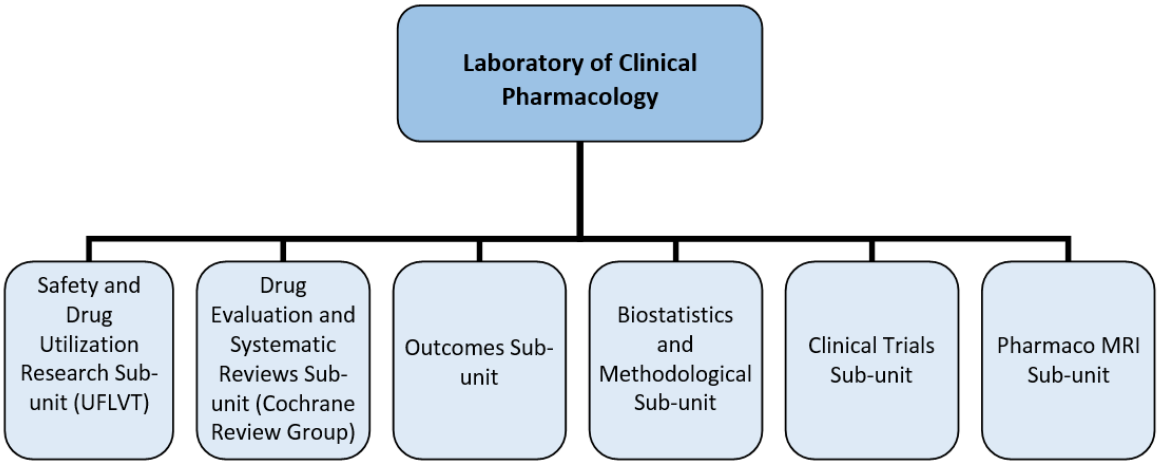

Figure 1 Structural organization of Laboratory of Clinical Pharmacology. Adapted from (1)
UFLVT, Unidade de Farmacovigilância de Lisboa e Vale do Tejo; *MRI*, Magnetic Resonance Imaging.

The main fields of interest for investigation in the LCP are clinical trials and the study of predictive biomarkers. It also provides services related to Clinical Pharmacology for research groups operating in HSM-CHLN, FMUL and IMM. In addition, it provides training in clinical trials conduction and Good Clinical Practices (GCP) and promotes collaborations with pharmaceutical companies and other research partners. The main research areas in LCP are neurodegenerative diseases, with a special focus on Alzheimer's disease and Huntington's disease; special populations, like paediatrics, rare diseases or late stage populations and "orphan" interventions. There is also an emphasis on outcomes research, development of systematic reviews and drug safety and utilization (1, 2).

According to the most recent scientific report of IMM (7), in 2014, the LCP accomplished 5 selected publications; had 6 ongoing research projects; 3 other important projects that started in 2013; 39 publications in peer-reviewed journals; 20 invited lectures and seminars; 18 communications in international conferences; 17 communications in national conferences;

participation in the organisation of 10 conferences; establishment of 2 research contracts with the industry ; 42 collaborations in advanced teaching; 7 collaboration works related to science and society and support in the execution of 8 MSc thesis (7).

1.1.1.1. Unidade de Farmacovigilância de Lisboa e Vale do Tejo

In my curricular internship, I had the opportunity to collaborate with the Safety and Drug Utilization Research sub-unit that corresponds to one of the four regional sections of the National Pharmacovigilance System - UFLVT. UFLVT's activities cover the population of the Portuguese capital and areas in the vicinity that, according to the Lisbon and Tagus Valley Regional Administration's activity report, corresponds to 3 659 868 inhabitants (8).

This sub-unit is responsible for the collection, management, reception and processing of adverse drug reactions (ADR) obtained through several means: e-mail, letter and phone. UFLVT also generates safety alert signals-periodic safety update reports. Pharmacovigilance activities include report collection, validation and follow-up, data management and quality management of procedures, which allows competent authorities to act in order to ensure the quality and safety of commercialized medicines (9).

UFLVT occupies a room inside the LCP facilities. Concerning physical resources, this room is equipped with material indispensable for the reception and processing of ADR notifications: three computers with access to internet, four secretaries, two phones, a scanner and a printer. One pharmacist and teaching assistant with qualifications in Pharmacovigilance, a Quality Manager and Pharmacovigilance technician and an administrative clerk compose the team that carries out UFLVT's daily activities. Medical direction is the responsibility of an HSM-CHLN physician, who is a specialist in Neurology. The unit frequently receives trainees to gain experience in pharmacovigilance.

1.1.1.2. Drug Evaluation and Systematic Reviews Sub-unit (Cochrane Review Group)

Cochrane is a global network composed by collaborators who produce credible health information through systematic reviews (10). This high-quality information can be found and accessed from the Cochrane Library, for anyone who needs to take health decisions founded on evidence-based medicine (11). The LCP is part of the Movement Disorders Cochrane Collaboration Review Group, whose expertise is in the conduction of systematic reviews and clinical trial methodology issues (10). This sub-unit has one administrative person responsible for all the issues

related to Cochrane systematic reviews. LCP has a group of professionals that work with the Cochrane review group.

1.1.1.3. Outcomes Sub-unit

The Outcomes sub-unit is focused on the study of measurement instruments, including biomarkers and patient reported outcomes in drug evaluation. This sub-unit is headed by an MD, PhD who works at the HSM-CHLN and who is a specialist in Paediatrics. In this unit, he designs and develops observational studies, meta-analysis and other research projects with a focus on the paediatric population. This sub-unit is the chamber of the investigator, where the project meetings occurred. Hence, the collaborators of this paediatrician frequently work in the open space of LCP.

1.1.1.4. Biostatistics and Methodological Sub-unit

The Biostatistics and Methodological sub-unit provides support in the design, implementation, analysis and reporting of clinical research studies and in the optimization of study design and feasibility. The sub-unit works in a room and in the open space of the LCP. The room is equipped with four computers and a library of several books about clinical pharmacology and neurology. The open space has also a cabinet with books and journals, two computers and two printers. The projects are developed by a multidisciplinary team, with specializations in biostatistics, project management and medical writing.

1.1.1.5. Clinical Trials Sub-unit

The facilities of the Clinical Trials sub-unit are part of the Neurology Department from the HSM-CHLN. It is headed by Professor Joaquim Ferreira and, through his efforts, this unit became a part of the LCP (2). The activity of the clinical trials sub-unit has been particularly important for the clinical research performed at the LCP. In the beginning, the main research area was movement disorders and, as a result, the group gained the sub-name of Movement Disorders, focusing only in the conduction of clinical trials in this area. However, throughout the years, the group expanded its capacities and became able and qualified to conduct clinical trials in other neurological disorders. Today, the centre develops clinical studies essentially in Parkinson's disease, Huntington's disease, Familial Amyloidotic Polyneuropathy (FAP), dystonia, multiple sclerosis, and Alzheimer's disease (2).

Patients have a central role in clinical research, and the proximity and attendance to potential participants increased since the Clinical Trials sub-unit is located in the Neurology Department. Potential candidates are identified in the outpatient clinic of the department. The execution of these clinical research projects also depends on the effort of an experienced multidisciplinary team that includes neurologists, psychiatrists, psychologists, nurses, speech therapists, study coordinators and other healthcare professionals. There is also a close link with the hospital pharmacy, namely the department of clinical trials, which is responsible for receiving, storing, and providing the drugs used in the clinical trials (12).

A clinical research unit need structure to operate according to GCPs. The sub-unit has a room for participants' examination, an office space equipped with computers, a room for the collection of biological material, a place to archive all the study's documentation and materials and a room for clinical data monitoring. The sub-unit also has facilities for the processing and storage of biologic samples (refrigeration capacity -20 ˚C and -70 ˚C). Nowadays, the procedures of one of the clinical trials taking place in centre are performed on the seventh floor of the hospital, where the recently inaugurated Centro de Investigação Clínica do Centro Académico de Medicina de Lisboa (CIC-CAML) is located. The creation of CIC-CAML has the objective to facilitate the design and conduct of early phase clinical trials and proof of concept studies, giving support to clinical research in the University Hospital (13).

1.1.1.6. Pharmaco Magnetic Resonance Imaging Sub-unit

The Pharmaco MRI sub-unit is another asset of the LCP. The main objective of this sub-unit is to develop projects in imagiology by magnetic resonance. In this sub-unit, neuroimaging techniques are used in the detection of micro-structural, functional and biochemical abnormalities in the central nervous system (7).

1.2. Training Objectives

I established some objectives to achieve with the execution of the different activities in the LCP and with the assistance of experienced health professionals. My primary objectives, which I defined *a priori*, are some skills that I consider critical to having a complete training on clinical research. I also defined secondary objectives throughout my internship, which relate to more specific skills and activities that I would like to accomplish, in order to complement my training. At the end of the training, I verified if I achieved my personal and professional goals.

1.2.1. Primary Objectives

The primary objectives defined in my internship were:

- To acquire knowledge, skills and qualifications in clinical studies' coordination, including empirical knowledge about all the activities associated with them;
- To understand the multidisciplinary character of a Clinical Research Unit and consequent development of certain personal, interpersonal and professional skills that will enable me to integrate the current labour market;
- To acquire the basic knowledge and skills in clinical data management and extraction, including quality control procedures, as well as in the writing of scientific documents;
- To understand the key concepts and procedures in pharmacovigilance and related areas of action in Portugal;
- To obtain specific working tools and techniques through the contact with experienced professionals;
- To apply and complement the theoretical background and skills acquired during the first year of my Master's Course and through the Biomedical Sciences Degree.

1.2.2. Secondary Objectives

The secondary objectives defined in my internship were:

- To prepare and support the conduction of clinical studies' visits taking place in the clinical trials sub-unit, updating the documentation relating to each study;
- To support the study team so as to comply with the protocol and all the processes associated with the clinical trials;
- To acquire a comprehensive understanding of a clinical research project's lifecycle;
- To support and monitor the various projects taking place in the LCP during the internship;
- To organize and manage clinical databases for statistical analysis;
- To write a paper related to the area of clinical trials, improving my medical writing skills;
- To be able to critically appraise the medical, scientific literature, including the methodology used in the elaboration of systematic reviews;
- To participate actively in the daily activities of the UFLVT, including reception, validation and autonomous processing of spontaneous reports of ADRs;

- To develop and improve personal and soft skills, such as communication, self-confidence, critical thinking, problem solving, time management, organisation, autonomy and responsibility;
- To identify potential areas of professional interest within the pharmaceutical industry and to establish a working contact network.

1.3. State-of-the-Art - Clinical Research and Clinical Trials

The pharmaceutical industry is nowadays the biggest investor in R&D (14). Clinical trials are part of R&D processes, constituting a set of advantages and benefits for stakeholders, which include the pharmaceutical industry, academic institutions and patients (14). The final goal of performing clinical trials is to test the effectiveness and safety of a new investigational medicinal product (IMP). However, the execution of clinical research has to assure that the rights, safety and well-being of participants are always protected (15). In this chapter, I will describe the current paradigm of the drug R&D process, the definition and different types of clinical trials, the process of implementation and conduction of clinical trials and the current position and hurdles faced by clinical trials and the pharmaceutical industry in the world and in Portugal.

1.3.1. Overview of Pharmaceutical Research and Development Process

The concept of clinical research covers the group of studies that involves humans, independent of their health status, or that uses the results of previous tests in humans as an object of study. It frequently appears related with pharmacological experimentation, conducted by the pharmaceutical industry or not (16). This patient-oriented research can include studies of mechanisms, therapies or interventions for human disease, studies to develop new medical technologies and clinical trials. Epidemiology and behavioural studies are also part of this concept, as well as outcomes and health services research (17).

The purpose of discovering, developing and bringing to clinical use new medicinal products is to prolong or improve patients' lives, by providing high quality health care (14). Its key contribution to global health is turning fundamental research into innovative treatments. The pharmaceutical industry and other stakeholders have been interested in minimizing the time and the cost needed to bring a compound from the scientific concept, through discovery and clinical development, to final regulatory approval and delivery to the patient. However, pharmaceutical R&D processes remain complex, time-consuming and very expensive (14, 18).

Some diseases like Alzheimer's, cancer, diabetes and human immunodeficiency virus require much more research and expertise to identify novel treatment targets. In recent years, due to advances in scientific and technological methods, innovative and powerful research tools have been emerging, making medicines' R&D more promising and challenging than before. As a result of the population's increased needs and of the methodological progresses, investigators face a progressively demanding clinical and regulatory environment, which requires more extensive collaboration (14). The global pharmaceutical market is growing, with sales reaching US $1.08 trillion in 2011 (19). The mature economies demonstrated this growth in a very slow way, but the growing economies were another matter. If this pattern continues, the market for medicines could be worth nearly US $1.6 trillion by 2020 (Figure 2) (19).

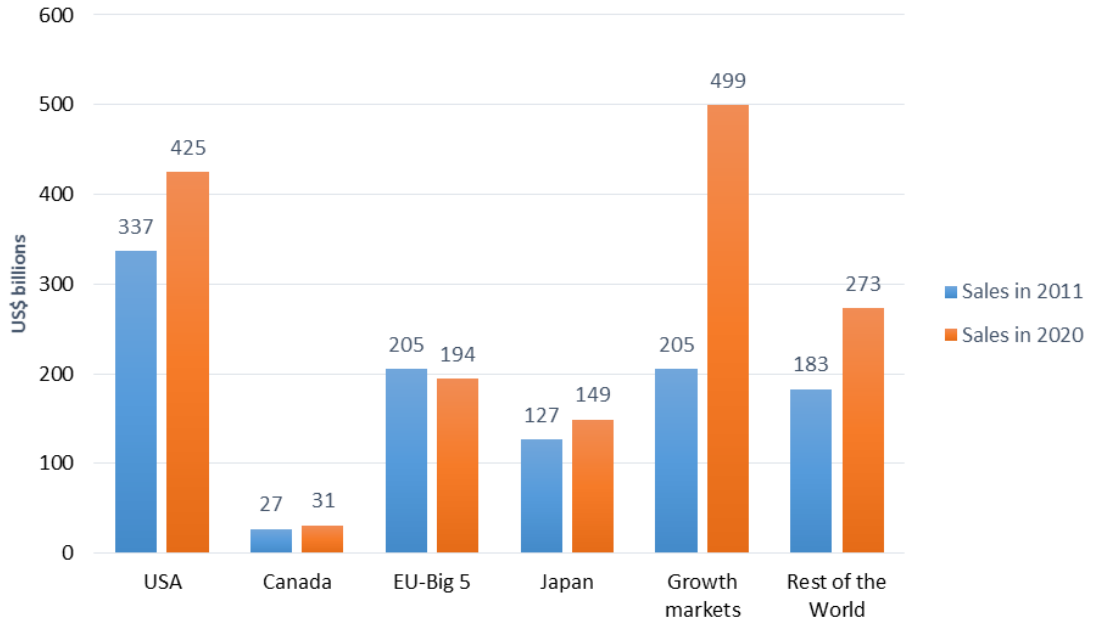

Figure 2 The global pharmaceutical market in 2011 and the estimate in 2020. Adapted from (19)
Growth markets: China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam; *EU-Big 5*: France, Germany, Italy, Spain and United Kingdom.

The pharmaceutical industry is the fifth largest industrial sector in Europe and accounted for 26.8% of the global pharmaceutical market in 2011, with an investment of €27.5 billion in R&D (20). According to the 2014 EU Industrial R&D Investment Scoreboard, the pharmaceuticals & biotechnology sector keeps the first position in the R&D ranking, maintaining a similar share of the total R&D investment (18.0%) (21). However, the combination of rising R&D costs, complex research areas, and regulatory requirements make the European Union (EU) a challenging

environment for healthcare innovation. Only 4% or €50 billion of the total health expenditure corresponds to R&D, while the remaining 96% or €1.4 trillion is spent on healthcare (22). Therefore, the continuously declining productivity of the pharmaceutical industry makes an overhaul of the R&D model more important than ever.

Companies often experience losses in terms of their R&D investments, because the high failure rates mark pharmaceutical R&D. Even if an early-phase compound seems to be promising, only preclinical and clinical trials will demonstrate its efficacy and safety. In addition, the later a failure occurs, the bigger may be the losses. A phase III failure is significantly more costly than a preclinical failure, because each phase is associated with a certain, compounded investment (23).

Demand for pharmaceutical products is rising, as the global population increases, ages and becomes more sedentary (19). This more demanding reimbursement environment raises the bar for pharmaceutical innovation, making it essential to release innovative products. However, the replacement power of current pharmaceutical companies' pipelines is compromised since the traditional fast follower and best-in-class strategies will not work anymore (24). Some progress has been made in recent years to address these challenges, including the adoption of an EU Regulation on clinical trials, an increase in the number of mergers, of licensing agreements and biotech acquisition of large biopharmaceutical companies, new research models coming to the fore that can make medicine development safer and more cost efficient (20).

The private sector produces nearly all the medicines on the market. When a pharmaceutical company invests in the R&D of new medicines, it starts by screening chemical and biological compounds that exhibit the potential for treating new or existing conditions. R&D begins once researchers identify a promising compound among, on average, 5 000–10 000 screened compounds (25). Researchers then extensively test the compound to ensure its efficacy and safety, a process that can take 10 to 15 years. It is a long, expensive and complex process, necessary to ensuring medicines meet the standards of quality, efficacy and safety (Figure 3). In 2012, 43 new medicines were launched and currently more than 7 000 compounds are at different stages of development, globally. The difference in these numbers highlights the many research hurdles to be overcome before compounds can be developed into safe and effective medicines (25).

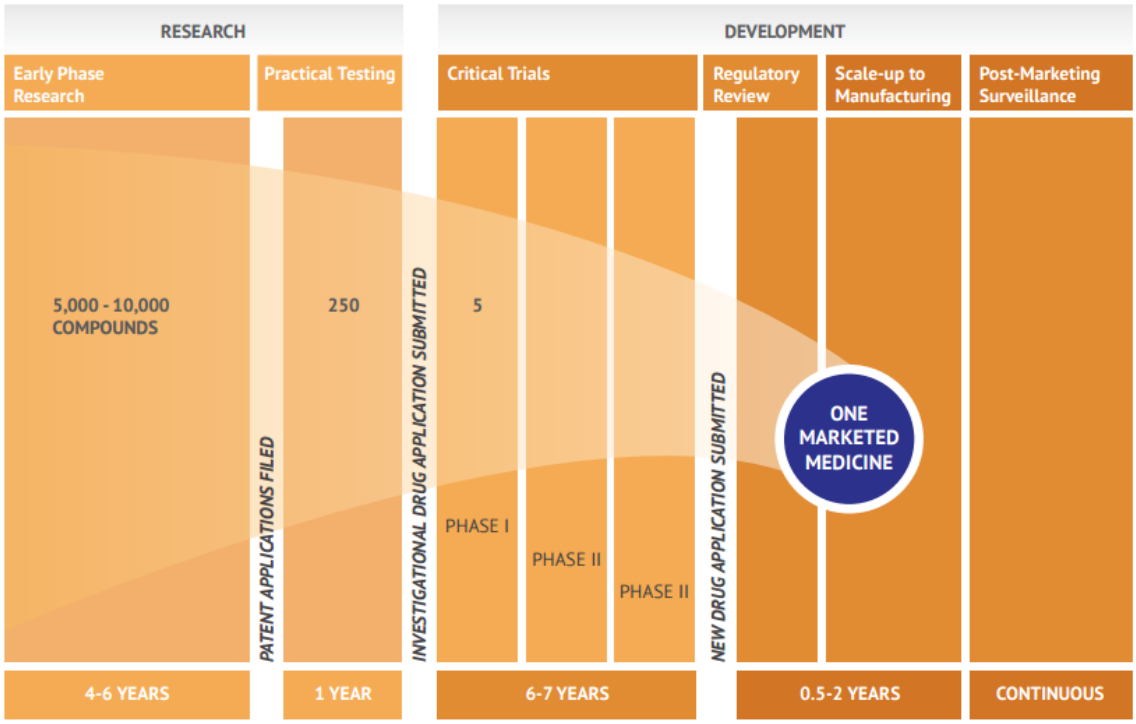

Figure 3 Pharmaceutical regulatory process. Adapted from (25)

Setting up a drug discovery and development program requires careful planning. It is essential to identify the characteristics of the IMP in the early stages of development and to plan an appropriate development based on this profile. The discovery process includes the early phases of research, which are designed to identify an IMP and to perform initial tests in the laboratory. This first stage takes approximately 4 to 6 years (Figure 3). By the end, investigators hope to identify a promising drug candidate to further study in the laboratory, in animal models, and, finally, in people (26).

The pre-clinical phase is dedicated to better understand the disease or condition in order to identify biological targets for a potential medicine and their role in disease. These studies are conducted in cells, tissues and animal models (25).

After learning more about the underlying disease pathway and identifying potential targets, investigators then seek to narrow the field of compounds to one lead compound that could influence the target and, possibly, become a drug (25). They do this in a variety of ways, including creating a molecule from living or synthetic material, using high-throughput screening methods to select a few promising possibilities from among thousands of potential candidates, identifying compounds found in nature, and using biotechnology to genetically engineer living

systems to produce disease-fighting molecules. Most pharmaceutical companies spend a very small percentage of their budgets on target selection and validation (19).

Even at this early stage of the research process, it is necessary to think about the final product, namely the route of administration, the formulation and the manufacturing process. Once one or more lead compounds are identified, pre-clinical tests are performed. Scientists carry out both in vitro and *in vivo* tests, using computer models, cells and animals. During this stage, scientists also must determine how to make large enough quantities of the drug to use in clinical trials. Techniques for making a drug on a small scale to use in this preclinical stage may not translate easily to larger production (25).

R&D in the pharmaceutical industry is moving towards open innovation, embracing increased collaboration and sharing of knowledge. The Innovative Medicines Initiative is one example of this, as the largest European public-private partnership in biomedical research that brings together diverse stakeholders, including patient groups and investigators. The funding system is balanced 1:1 and the founding organisations of this entity are the European Federation of Pharmaceutical Industries and Associations and the European Commission. The central aims of the Innovative Medicines Initiative are to enhance safety and efficacy of therapies for the major diseases, as well as to improve knowledge management and education in R&D (20, 27).

1.3.2. Clinical Trial Concept

A clinical research study is an investigation that directly involves a particular person or a group of people or that uses materials from humans, such as their behaviour or samples of their tissues. The aims of these studies are to determine or confirm clinical, pharmacological or other pharmacodynamics effects of medical products, to identify any adverse reactions related to the IMP or to study the pharmacokinetic processes of one or more IMP. The final purpose is to establish their safety and/or efficacy profiles (28).

Clinical studies may involve the study of a product that changes, influences or programs the health care, behaviour or knowledge of participants or caregivers, in order to discover or verify their health effects – interventional clinical study. On the other hand, participants may be part of interventions (which can include medical products such as drugs or devices) or procedures during their routine medical care – observational clinical study. All clinical studies, independently of the need of intervention or not, have to be designed, conducted, recorded and reported and its results revised and disclosed in accordance with the principles of GCP (29, 30).

A clinical trial is a type of interventional clinical study. The Randomized Controlled Trial (RCT) is considered the gold standard in terms of clinical trial design. As clinical trials are intended to discover or verify the security and efficacy of one or more IMPs, they are a long and careful process that may take many years to complete. Strictly following a pre-defined research protocol, the assignment of a subject to a particular therapeutic intervention is decided in advance and does not fall within normal clinical practice. The investigators also apply other diagnostic or monitoring procedures to the participants, in addition to normal clinical practice (29).

Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo, or to no intervention. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different from available alternatives (including no intervention). The assessments of safety and efficacy are performed by measuring certain outcomes. Clinical trials, compared to observational studies, are considered by many to be the reference method for evaluation of healthcare interventions (28, 30).

The concept of clinical trial has also changed according to the events occurring in clinical research over the years. The concept of clinical trial began to be refined and adjusted with James Lind's Scurvy Trial, in 1747 (31). This physician conducted a controlled trial on a ship to evaluate the most promising cure for scurvy. Lind chose twelve patients with similar manifestations of the disease and with one diet in common. Afterwards, he administered to each two of them, one of the alternative therapeutic regimens. At the end, Lind analysed the treatment that had produced the best results (31). In the 19th century, the concept of emerged, marking yet another important milestone in the history of modern clinical trials. The concept of randomization was introduced into clinical trials in 1923. Blind clinical trials, where neither group knows which treatment they are receiving, emerged when the first double blind comparative trial was performed to investigate patulin treatment for common cold. Multicentre clinical trials where multiple studies were conducted at various sites all using the same protocol to provide wider testing and better statistical data, were introduced, in 1946, when the first RCT of streptomycin in pulmonary tuberculosis was conducted (31).

1.3.2.1. Ethical and Regulatory Framework

Clinical research is a highly regulated area. All the activities related to the implementation and conduction of clinical trials follow ethical codes and important policies, directives and recommendations. The most important documents are the Declaration of Helsinki, the GCP of the International Conference on Harmonisation of Technical Requirements for Registration of

Pharmaceuticals for Human Use (ICH), the 2001/20/CE Directive, the 2005/28/CE Directive, and the 95/46/CE Directive.

The biggest advances in protection for human subjects have been a response to human abuses. The World War II experiments were an example of unethical research. The Nuremberg Code appeared in 1947 and it was the first International Guidance on the ethics of medical research involving subjects. This document highlighted the importance of obtaining voluntary, informed consent from research participants. In 1948, the Universal Declaration of Human Rights expressed concern about the rights of human beings that were subjected to involuntary harm. The confrontation with the thalidomide disaster reinforced federal oversight of drug testing, including a requirement for informed consent (32).

In 1964, in Helsinki, the World Medical Association articulated general principles and specific guidelines on the use of human subjects in medical research, creating the Declaration of Helsinki. The Declaration of Helsinki has been undergoing changes every few years. The last revision included increased protections for vulnerable populations, new provisions for research-related injury compensations, and post-study requirements for reporting results to participants and providing access to any potential treatments that arise from the study. Despite not being a legally obligatory document, it is one of the most influential ethical guides in the history of human research (33).

GCP has become the universal standard for ethical conduct of clinical trials. This guideline is valid in the EU, Japan and United States of America (USA) (15). For clinical research with medical devices in human subjects, the International Organization for Standardization (ISO) created the ISO 14155:2011. These international standards are transposed into legal requirements of laws and regulations by each national authority (34).

Regulatory entities such as the European Medicines Agency (EMA) and the Food and Drug Administration, in the USA, are responsible for establishing procedures and rules for drug testing and for guaranteeing their implementation. In parallel to ethical guidelines, clinical trials started to become included in the legislation, with the aim of create an environment that was favourable for conducting clinical trials, with the highest standards of patient safety, for all EU member states. The 2001/20/EC Directive describes the requirements for the conduction of clinical trials with drugs for human use performed by the pharmaceutical industry and by academic institutions in EU. In 2004, this directive was transposed into the national legislation by Law No. 46/2004 of 19th of August, which additionally established the Ethics Committee for Clinical Research - Comissão de Ética para a Investigação Clínica (CEIC) and was later repealed by a Law No. 21/2014

of 16th of April (35). Law No. 21/2014 – Clinical Research Law - covers all clinical research conducted in Portugal with humans, including not only clinical trials with IMPs for human use but also studies with medical devices, cosmetics, food supplements and observational studies. This law created the National Ethics Committees Network (coordinated by CEIC), a National Portal for the register of all clinical research, and a clinical trials database. This law was amended last year by Law No. 73/2015 of 27th of July that establishes the conditions under which the monitors, auditors and inspectors can access the records of clinical trials' participants (29, 36).

At the European level, Regulation No. 536/2014 of the European Parliament and of the Council of 16th of April, 2014, related to clinical trials of medicinal products for human use, was issued, repealing the 2001/20/EC Directive. This legislation will be directly applicable to the legal framework of the member states six months after publication in the Official Journal of the European Communities. This publication is a notice of operational compliance of the Union portal and the EU database, emitted by the European Commission. This regulation shall apply only to events occurred after 28th May 2016 (35).

The 2005/28/CE Directive lays the principles and guidelines for GCP as applicable to investigational medicines for human use, and the requirements for the authorisation of their manufacture and importation. This directive was transposed into the Portuguese Decree-Law No. 102/2007 of 2nd of April.

Another legislation to be observed is the 95/46/CE Directive on the protection of personal data, transposed to the Portuguese Law no. 67/98 of 26th of October and by the Deliberation No. 333/2007 of the National Data Protection Authority - Comissão Nacional de Proteção de Dados (CNPD).

Comparing to the USA, the EU presents the disadvantage of not having a European organisation for financing and promoting clinical research projects in the health area, as is the case of National Institute of Health (12, 37).

1.3.2.2.Setting up and Running a Clinical Trial

It can take up to 13 years to take a medicine from its origins as a molecule to a treatment with tangible benefits for patients (38). In this section, I will describe the steps needed to complete this process, which will help explain why it is so time-consuming.

Drug development is ideally a logical, stepwise procedure in which information from small early studies is used to support and plan later, larger, more definitive studies, called clinical trials (38). When the truly development process is initiated, we can divide it in four temporal phases

(Phase I-IV). However, this classification provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases. According to the guideline ICH E8, a classification system using study objectives is preferable. The “phase” concept is a description, not a set of requirements. Thus, the temporal phases do not imply a fixed order of studies, since for some drugs in a development plan, the typical sequence will not be appropriate or necessary (26).

Specifically, there are four temporal phases of development that correspond to the kind of studies usually performed:

- **Phase I (Human Pharmacology)** – in this stage, the candidate drug is tested in people for the first time – *first-in-man* studies. Studies are usually conducted with a small number of healthy volunteers, generally from 20 to 100. The main goal of a Phase I trial is to assess the safety of the medicine in humans, determining the safe dosing range and if the candidate drug should move on to the next stage of development. The dose is gradually increased during this period to allow the investigator to measure the participant's clinical response to the drug (pharmacokinetics). They also study which dosage levels are safe and well tolerated (pharmacodynamics) (26).

- **Phase II (Therapeutic Exploratory)** - investigators evaluate the candidate drug’s efficacy in about 100 to 500 patients with the disease. Initial therapeutic exploratory studies may use a variety of study designs. Many Phase II study patients receiving the drug compared with patients receiving a different treatment, either an inactive substance (placebo), or a different drug that is usually considered the standard of care for the disease. In this phase, researchers work to determine the most effective dosages and the best formulation, examining the possible short-term adverse events (AE) and risks associated with the drug. They also evaluate some potential study endpoints, therapeutic regimens and target populations. If the drug continues to show promise, it is prepared for the much larger Phase III trials (26).

- **Phase III (Therapeutic Confirmatory)** – in this phase the potential drug is tested in about 1000 to 5000 patients to generate statistically significant data about safety, effectiveness and the overall benefit-risk relationship. Phase III is used to test the results of earlier trials in larger populations and to demonstrate or confirm the therapeutic benefit. This phase generally provides the basis for the benefit-risk assessment for the new medicine and

much of the core instructions to help ensure proper use of the drug, like information on potential drug-drug interactions and specific dosing instructions (26).

- **Phase IV (Therapeutic Use)** – in this period, all studies are performed after drug approval and are related to the approved indication. Despite these studies not being considered necessary for approval, they are often important for optimising the drug's use through the assessment of long-term safety or effects in specific patient subgroups. They may be of any type but should have valid scientific objectives. Through these studies it is possible to collect additional information about drug-drug interaction, dose-response or safety (26).

The rigorous planning and design of a clinical trial, taking into consideration certain key aspects, is crucial to generate meaningful results. It involves deciding parameters such as the patient population to be studied and the length of the trial, the treatment(s) to be investigated, taking into account current treatments, the outcomes and the methodologies by which the trial will be conducted (38).

To be included in a clinical trial, patients must meet specific criteria (38). Among the common criteria are the existence of a particular disease or treatment history, and the fact that the participants belong to a certain age group (38). These eligibility criteria help ensure that the people in the trial are as similar as possible to each other, with respect to basic profile, type and stage of disease. It also ensures that the results of any treatment effect are associated as much as possible with the drug being studied, instead of other factors. Clinical trials are frequently controlled, that is, the agent or regimen being tested is compared with a control. This control may be either a medically ineffectual treatment known as a placebo (if no effective therapies are available for the disease being studied) or a standard treatment, that should be one widely used and with demonstrated effectivity at the time the trial was designed. Some trials take several years to complete and because of this, the standard treatment may no longer be the best available therapeutic choice (38).

The aim of a clinical trial is to measure key outcomes and to test the clinical efficacy and tolerability of the treatment in a particular disease. The trial will usually specify a primary outcome, typically to assess the treatment efficacy. Usually, if that outcome is verified during the trial, it means a positive result for the study and the treatment being tested. A trial may also define one or more secondary outcomes, which normally include secondary efficacy measures and safety parameters. The clinical trial protocol provides the design for the study conduct and

sets out the outcomes of the study. It explicitly states how and when to measure and evaluate these outcomes (38).

In phase III and some phase II trials, the patient population may be randomized (randomly allocated to receive one or other of the alternative treatments being studied) and stratified (partitioned by a factor other than the treatment, often to ensure that equal numbers of participants with a characteristic thought to affect prognosis or response to the intervention will be allocated to each comparison group) (39).

In practice, there are issues to take into count before starting a clinical trial (40). One of the first steps for running a clinical trial is the licensing approval. The investigators should compile the information and results from all the performed studies as well as a description of the medicine's manufacturing process and submit this information to the regulatory agencies in order to demonstrate the safety and effectiveness of the new medicine. In order to perform clinical trials in Portugal, sponsors have to get authorization from the Competent Authority and ethical approval from CEIC plus approval from the CNPD. The application to the ethics committee, to the competent authority and to CNPD may be submitted in parallel, or in any order (40).

During the approval process, there is no procedural interaction between the competent authority and the national or local research ethics committee (40). Nevertheless, all of them can request it. Once it has been concluded that a medicine is safe and effective, its value and cost-effectiveness must be assessed. Health technology assessment processes are used by the relevant regulatory body to assess the added value of medicines and make decisions on access. Depending on the given healthcare system, health technology assessments can be used to determine pricing, reimbursement status, and/or prescription status (40). Once a drug is licensed for use and pricing and reimbursement measures determined, it may be made available for patients. Even after a drug is on the market, it is being scrutinized: post-approval or post-marketing studies are necessary to monitor a drug's long-term effects (40).

1.3.2.3. Clinical Trials in the World and in Portugal

The clinical trials database – ClinicalTrials.gov - contains the registry of all clinical studies performed in the world. In 2000, the number of registered clinical trials was 5 634. On February of 2016, the number of registered clinical trials is 208 114, with a growing trend observed over the years (41). The region with the biggest percentage of studies is North America (in particular the USA – 90 684 studies) followed by Europe (58 269 studies). Eighty percent are interventional studies, with the majority of them intended to test a drug or biologic product (41, 42).

In Europe, approximately 4 400 clinical trials are applied for, every year (43). However, Europe has been losing competitiveness comparing with other regions of the world (44). According to EudraCT, in 2015, approximately 80% of clinical trials were sponsored by the pharmaceutical industry and 20% by non-commercial sponsors. EudraCT is a database of all the interventional clinical trials with medicinal products in the EU, submitted to the ethics committee and competent authority, starting on the 1st of May, 2004 (Figure 4) (45).

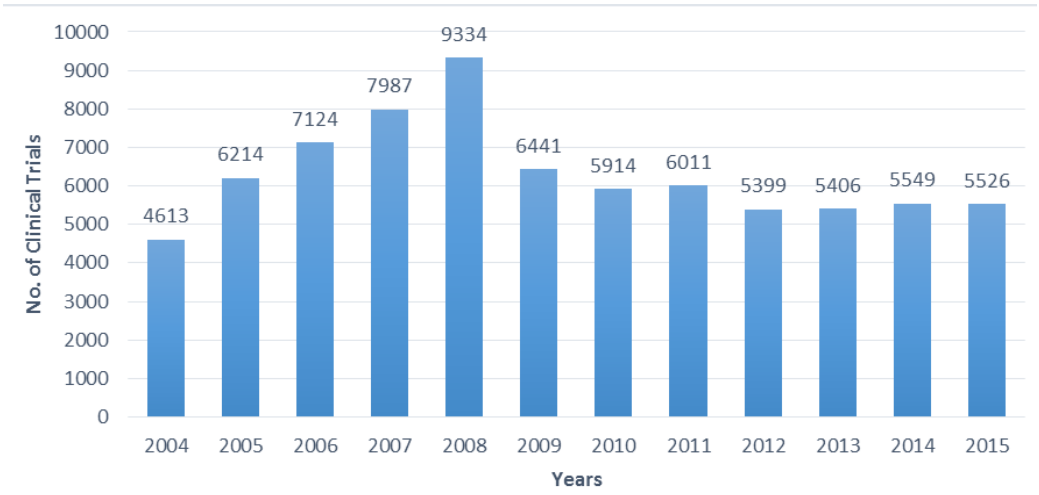

Figure 4 Total of EudraCT Numbers each year in the EudraCT Database, from 2004 to 2015. Adapted from (45)

In the past, it was observed a decrease in the productivity and quality of clinical trials, in Portugal. According to INFARMED's statistics, clinical trials in Portugal decreased in number between 2008 and 2011, with the number of submitted clinical trials went from 146 to 88 (Figure 5)(46).

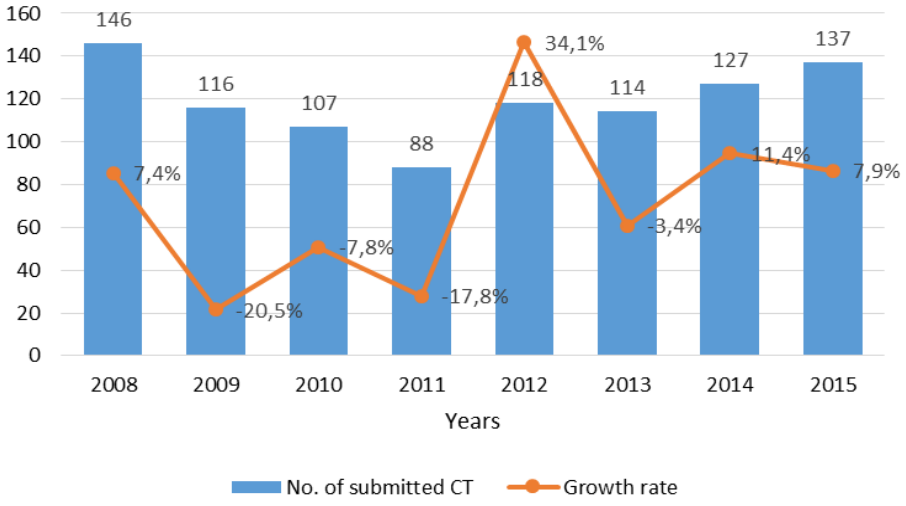

Figure 5 Number and growth rate of clinical trials submitted in Portugal between 2008 and 2015. Adapted from (46)

This decline was due to several factors, like the lack of policies to promote clinical research in Portugal, the low number of infrastructures to perform clinical research in clinical centres and the devaluation of clinical research in medical curricula (12). However, in the last three years, this tendency seems to have changed, with 137 clinical trials submitted in 2015 (46).

The majority of these studies are phase III clinical trials and the most explored therapeutic area is oncology, with the majority of drug candidates being antineoplastic and immunomodulating agents (Figure 6).

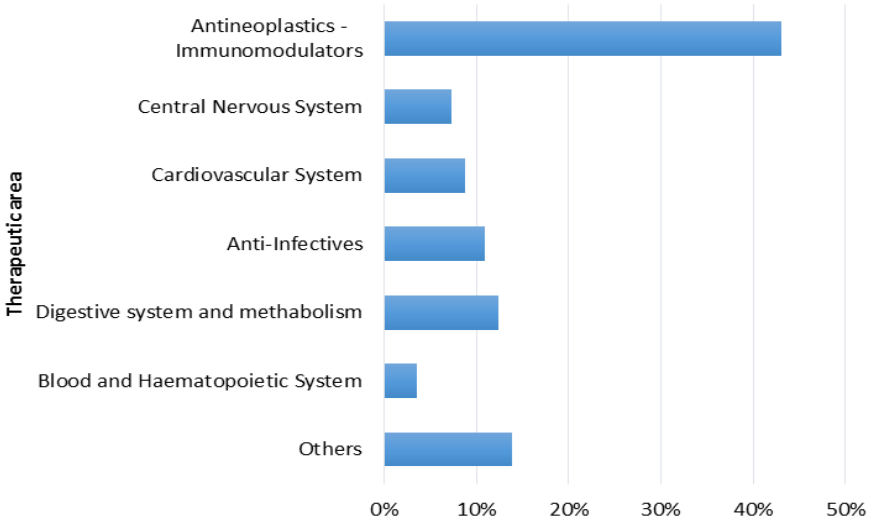

Figure 6 Percentage of clinical trials by therapeutic area, in 2015, in Portugal. Adapted from (46)

The funding of clinical trials in Portugal is mainly in the hands of the pharmaceutical industry, which is complemented by a small number of non-commercial clinical trials (44).

Neurology is one of the areas where the investment per participant is higher (44). Moreover, it is estimated that more than 600 disorders afflict the nervous system (47). Neurodegenerative diseases are hereditary and sporadic conditions, characterized by progressive nervous system dysfunction. These disorders are often associated with the atrophy of the affected central or peripheral structures of the nervous system and include diseases such as Alzheimer's disease and other dementias, genetic brain disorders, Parkinson's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Huntington's disease, and others. In the last years, people have had access to better health care services, which increased the average life expectancy and to an aging population. The elderly are the age group with more incidences of dementia and other neurological diseases, which consequently affects their quality of life. Thus, it becomes indispensable to find new therapies and approaches to relieve symptoms (47).

The Associação Portuguesa da Indústria Farmacêutica conducted a pilot study in 2012 with the objective of quantifying the investment potential not used by Portugal, through an evaluation of pharmaceutical companies that performed clinical trials in our country. The preliminary results of this study showed that neurology was the clinical area with the second highest investment in clinical trials, surpassed only by oncology (44).

2. On the Job Training

The "On the Job Training" section is dedicated to the presentation of the different activities that I performed during my internship. I will present two Gantt charts: one with a chronological sequence of my internship in the LCP sub-units and the other with the periods during which I collaborated in different clinical research activities.

My internship can be divided into four phases that correspond to the periods during which I frequented the different LCP sub-units (Figure 7).

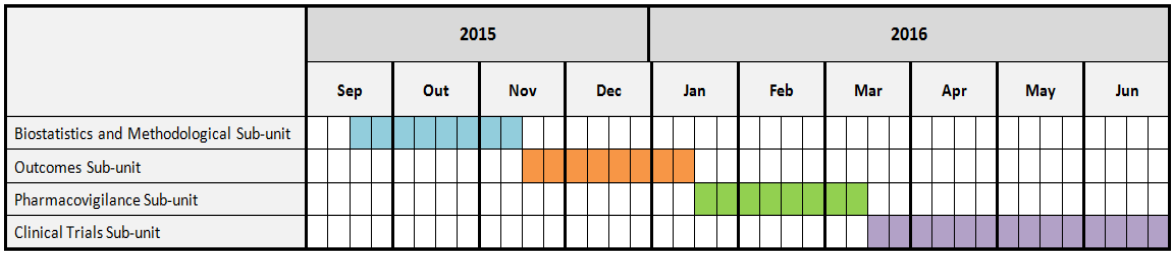

Figure 7 Gantt chart with the schedule of my collaboration in the LCP sub-units.

In the first phase, which marked the beginning of my internship (from September 2015 to November 2015) at the LCP, I worked mostly in data management and medical writing projects, in the areas of cardiology and clinical pharmacology. In the second part, which lasted two months, I developed projects at the Outcomes sub-unit, collaborating in the execution of meta-analysis and in project management and monitoring of an observational study in paediatrics. The third phase involved pharmacovigilance and drug safety quality control activities, developed at the UFLVT from January 2016 to March 2016. From March to the end of my internship, I had the opportunity to work as a study coordinator in several studies at the Clinical Trials sub unit. Despite this temporal division by different research activities, I remained active in medical writing and in other academia research projects during almost all the internship (Figure 8).

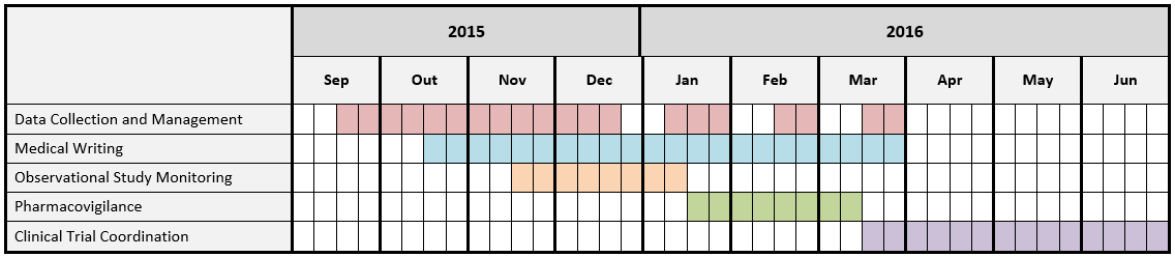

Figure 8 Gantt chart with the activities developed during the internship.

2.1. Specific Training

2.1.1. Clinical Trials Sub-unit Overview

The last three months of my internship were spent at the Clinical Trials sub-unit. In this subsection, I will describe the specific experience acquired during this part of the training and all the activities that I performed, mainly as a study coordinator. The Clinical Trials sub-unit is dedicated to clinical research coordination, and to conducting clinical trials and non-interventional studies, with a major focus on phase II and III clinical trials in neurodegenerative disorders.

The activities performed at the Clinical trials sub-unit involve many stakeholders. Thus, to ensure data confidentiality, as well as the safety, rights and well-being of patients, during my internship I had to consider some guidelines and relevant legislation in clinical research, independently of the study involved. Since I generated data that was intended to be submitted to regulatory authorities, I understood that it was essential to follow all the regulatory requirements. During this time, I worked under the close guidance of two senior study coordinators, and alongside colleagues from my Master's programme.

In the first week of the internship, the experienced study coordinators gave me a full overview of the clinical site, the procedures in place and some points about the studies that I would coordinate more closely. I also learnt where the material was stored, and the general workflow of the centre, amongst many other aspects. 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, as well as who the Principal Investigator (PI) and the Clinical Research Associates (CRA) of each trial were. Every team member had very specific roles, which I had to become acquainted with. Some of the studies that took place in the unit were initiated after my training began, others were completed during the training, and others were finished earlier. Thus, I did not closely accompany all these studies.

Throughout the internship, I received training in areas and procedures that are common to almost all clinical trials. These include: the compliance with the procedures stated in the protocol, the measurement of vital signs, the processing of laboratory samples and the filling of electronic Case Report Forms (eCRFs). Despite this and to facilitate the work in the centre, I was allocated to specific studies, and, for this reason, I worked full time with particular neurologic conditions: FAP, Huntington's disease and Parkinson's disease. Answering to queries and questions about the clinical trial and organizing the studies' documents are examples of specific

activities that I was responsible for. Despite the majority of them being clinical trials, I also followed the conduction of two observational studies. A summary of the clinical trials and the observational studies that I participated in as a coordinator is presented on Table 1.

Table 1 Clinical studies that I coordinated more actively in Clinical Trials sub-unit.

Study designation	Phase	Condition	Study design	Intervention
ALN-TTR02-004	Phase 3	FAP	Double blind	Patisiran
ALN-TTR02-006	Extension phase	FAP	Open label	Patisiran
ISIS CS2	Phase 3	FAP	Double-blind	IONIS-TTR Rx
ISIS CS3	Extension phase	FAP	Open-label	IONIS-TTR Rx
LEGATO-HD	Phase 2	Hungtinton's disease	Double-blind	Laquinimod
DUODOPA	Phase 2	Parkinson's disease	Open label	Duodopa
ACADIA	Phase 3	Parkinson's disease psychosis	Double-blind	Pimavanserin
ENGAGE	Phase 3	Alzheimer's disease	Double-blind	Aducanumab
INTEREST	Observational	Idiopatic Cervical Dystonia	Prospective Cohort	Botulinum toxin type A
REGISTRY	Observational	Huntington's disease	Prospective Cohort	-

FAP, Familial Amyloidotic Polyneuropathy

Because of the frequency of the study procedures in the site, there were two studies where I participated more actively, both about FAP, which I will detail below.

- **ALN-TTR02**

ALN-TTR02-004 (*APOLLO: The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis*) is a phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of patisiran in subjects with FAP. This study, sponsored by Alnylam Pharmaceuticals, is currently ongoing, having recruited 225 participants of several countries, aged 18 -85 years, of both genders and with a diagnosis of FAP. These participants were randomized to receive either

patisiran or placebo, which have been administered by intravenous infusion. In TTR02-004, the administration of patisiran or placebo occurs every 3 weeks for up to 18 months (48, 49).

ALN-TTR02-006 (*The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis in Patients Who Have Already Been Treated With ALN-TTR02 (Patisiran)*) is a multicenter, open-label, extension study to evaluate the long-term safety and efficacy of patisiran in patients with FAP who have completed a prior clinical study with patisiran and meet certain eligibility criteria, namely having completed the last efficacy visit in the parent study (ALN-TTR02-004) and, in the opinion of the investigator, tolerated study drug. In this extension phase, approximately 228 participants, that will receive patisiran administered by intravenous infusion, are expected to be recruited (49, 50).

- **ISIS 420915**

ISIS 420915-CS2 (*Efficacy and Safety of IONIS-TTR Rx in FAP*) is a phase II/III, randomized, double-blind, placebo-controlled clinical trial. It aims to assess the efficacy and safety of ISIS 420915 in subjects with FAP. This study is sponsored by Ionis Pharmaceuticals, Inc. and recruited 172 participants with early to mid-stage neuropathy, aged 18 and 82 years, of both genders. To be included in this clinical trial, the subjects had to be in late stage 1 or early stage 2 of the disease. Patients received either IONIS-TTR Rx or placebo for 65 weeks. IMP or placebo were administered subcutaneously 3 times on alternate days in the first week and then once-weekly for 64 weeks (51).

ISIS 420915-CS3 (*Open-Label Extension Assessing Long Term Safety and Efficacy of IONIS-TTR Rx in FAP*) is an open-label extension study, that is now recruiting patients who satisfactorily completed the dosing and efficacy assessments in ISIS 420915-CS2. It aims to assess the long-term safety and efficacy of ISIS 420915 in patients with FAP. IONIS-TTR Rx is administered once weekly (52, 53).

Beside the above-mentioned studies, I also participated in other interventional and observational studies (Table 1). However, most of them required less visits and involved simpler procedures. In the observational studies, the principal coordination activities were to provide the patient's dossier to the investigator and enter data into the CRF.

2.1.2. General Procedures in Clinical Trials Sub-unit

- **Compliance management**

Compliance with the study protocol is imperative, because it helps to ensure that the collected results are accurate and scientifically rigorous. During my training in study coordination, it was necessary for me to be acquainted with the protocol, including knowing the study objectives, proceedings and timelines, eligibility criteria, data confidentiality and participants' protection rules. Once I understood the protocols, I was able to collaborate in the visit procedures of several clinical trials. After the investigators find a potential candidate and the patient is included in the study, according to the protocol procedures, the patient could have to visit the site according to the protocol's assessment schedule. Thus, I received training in scheduling the study visits with the patient or with his caregiver, taking into consideration the timelines required by the protocol and the participant's availability. These routine visits were frequently scheduled either by the investigator, or by the study coordinator. For each visit, I was instructed to read what the protocol required, and prepare in accordance with the sponsor's and authorities' standards.

- **Measurement of vital signs**

Although the measurement of vital signs is not an official task of a study coordinator, this is a characteristic procedure of all studies in some of their schedule visits. Since I accompanied participants during their entire visit period in the centre, I was authorized to measure and register vital signs. This included the assessment of blood pressure, pulse, temperature and respiratory rate. This procedure was frequently done in the beginning of the visit, before the participant was observed by the other research members that did other procedures. The training I received allowed me to do these simple procedures and collect this data when the protocol required it.

- **Processing of laboratory samples**

Each clinical trial had a laboratory manual, providing instructions on how to collect, handle, process, and ship the required biological samples. Human biological samples are all biological material of human origin, which includes organs, tissues, and bodily fluids like blood and its derivatives (54).

The collection of laboratory samples was a mandatory procedure of almost all clinical trials, since the data provided through the analysis of these samples is an important source of

information for the continuity of the study. Frequently, the participant is required to cooperate with the collection of urine and blood during site visits, with the intervention of an experienced laboratory technician for the collection of blood. After that, the participant gives the urine and/or blood samples to the study coordinator that processes them according to the laboratory manual of the correspondent study. This usually means allowing some time to pass for the blood to clot, and then centrifuging the tubes. After centrifugation is complete, the plasma is transferred to the transfer tubes. The central laboratory of each trial provided a custom requisition and all the equipment necessary for storing and sending the biological samples. As a study coordinator trainee, I had to ensure the correct labelling, temperature-controlled stability, packaging and delivery of human biologic samples in order to obtain quality data of periodic safety assessments.

The shipping of samples was done either in ambient temperature or in dry ice. For visits that 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 pick-up. After the samples arrive to the laboratory, the results are provided. Because the collection of biologic samples must comply with ethical and transparency codes, the participant had to give informed consent for the collection of his or her biologic samples and to be informed about the potential future use of the samples and about the dissemination of research results (54).

- **Organizing documentation**

As a study coordinator, I was also responsible for the organization and management of the studies' documentation. In this sub-unit, each study had a specific cabinet, where its documents were safely archived and properly organized. However, the basic features were similar for all studies, like the participants' dossiers and the Investigator Site File (ISF), where all information concerning the clinical trial is available, including the study protocol, contact information, financial agreements, and study manuals, among others. In these cabinets, we also kept some specific study equipment like tablets, dossiers with scales and other necessary documentation for the visits. During my internship, I understood the importance of organizing all the documents and materials related with the study. The validation of the procedures required per protocol involves the reporting of that data in a physical and electronic support. The information could go missing if these supports were lost or not well organized; it is a risk for the quality and viability of the study.

- **e-CRF filling**

Case Report Form (CRF) is a specialized document, where all data of each clinical trial participant have to be recorded. It should be study protocol driven, robust in content and it has to easily allow the entry of data. Despite paper CRFs still being used, electronic CRFs offer certain advantages, such as the improvement of data quality, online discrepancy management and faster database lock. At the Clinical Trials sub-unit, all studies had eCRFs.

There were specific eCRF platforms for each clinical trial, such that I had to learn how to manage different types of eCRFs. The site study coordinators taught me how to access each eCRF and to entry the data as well as to validate, correct and answer queries, according to GCP. I could work with the following electronic systems: Inform™, BioClinica®, Viedoc™, and Oracle™.

In addition, I received training about the systems responsible for IMP allocation and prescription. Some clinical trials had Interactive Voice Response System (IVRS) and other Interactive Web Response System (IWRS), and I learnt how to use both. The importance of data confidentiality when accessing the different eCRFs was also made clear during the initial training.

2.1.3. Clinical Studies' Specific Activities

After my initial training in these general activities of coordination, I started being part of the specific activities in place at the centre. The initial training was essential so I could do an efficient job in the clinical trial specific activities, such as preparing patient appointments and answering queries. While each trial is different, there were many procedures common to all of them. I will describe some of the more specific, trial-related activities I did.

- **Feasibility Phase**

The feasibility phase is one of the first steps in clinical trial conduction and it is composed by a set of site visits and contacts, with the objective of ensuring that the clinical site meets all the necessary requisites to carry out the clinical trial. The sponsor contacts the PI, in order to understand his interest in conducting the study. Then, a feasibility questionnaire is sent with the objective of evaluating the clinical research site conditions and PI availability. The PI and the study coordinators schedule a meeting to fill it in, where the main characteristics, challenges and requirements of the study are also discussed.

By filling in this questionnaire, the PI should provide some specific information, which includes data about the site's experience in clinical research, the target disease, resources and

facilities available, and who the person of contact is, in case of additional questions. After all this information is sent back to the sponsor, the site waits for a feedback. If the sponsor/Clinical Research Organization (CRO) agrees on the implementation of the study at the site, a face-to-face feasibility visit is scheduled. During this visit, the PI, a study coordinator, and sometimes the pharmacy staff, must be available. The sponsor/CRO usually requests a tour of the facility and time to discuss the basic elements of the protocol and how these are related to the feasibility of recruiting potential participants.

In this pre-study visit the PI responsibilities are usually discussed; the necessary qualifications of study team members; the study objectives and outcomes; the procedures required in the protocol; the eligibility criteria, and patient recruitment strategies; ethic issues, like the approval timelines from the Administration Board of the HSM-CHLN and from the Ethics Committee; AE reporting; source documentation, and record retention. In this phase the space requirements, availability of a secure area to store IMP or devices and the availability of required equipment are also assessed. During my training, some feasibility meetings occurred in the unit. Although I did not participate actively in any, I consider that it is an important topic to understand the study implementation route.

- **Investigators' Meeting**

The investigators' meetings are appointments with the purpose of training the members involved in the conduction of the clinical trial on all aspects of the protocol. The study team members required to be present this meeting usually include the monitor/CRA, the PI, co-the Investigators, the study coordinator(s), the health technicians, and the quality managers. They receive training on GCP, the study protocol, the required procedures, and how to manage correctly the study equipment and software. The members present can ask questions and make comments during the meeting. I did not attend any investigators' meeting because I was a trainee and only the principal study coordinators were authorised to participate. Sometimes this meeting counts as the initiation visit, meaning that when the study members return to the site, they are ready to screen their first subject. However, I will describe in the next topic a site initiation visit as a separate step.

- **Site Initiation Visit**

The site initiation visit is crucial because it is the last step before the sponsor activates the study side for enrolment. After the clinical site facilities are evaluated and qualified, all regulatory

requirements have been completed, the Ethics Committee approval obtained and the investigators have been enlightened about the clinical trial, it is necessary to schedule a meeting between the sponsor, the CRA and the study team. Thus, all the elements involved in the clinical trial receive adequate training from the sponsor/CRO. This meeting involves an explanation about the study rationale, distribution of study material and discussion of some important issues, procedures and screening schedules. It is also the opportunity for the sponsor/CRO to ensure that the investigator fully understands his or her responsibilities. The monitor usually visits the infrastructures of the site and verifies if any extra equipment is needed. The main preoccupation is to ensure the good condition of the pharmacy, and the equipment to process and store the biological samples.

During my internship, I had the opportunity to attend one site initiation visit, wherein the sponsor and the CRA explained the clinical trial to study team.

Some topics discussed during the site initiation visit included:

- Investigator's Brochure;
- Study Protocol;
- Clinical trial design;
- Inclusion and Exclusion Criteria;
- Informed Consent Form (ICF);
- IMP characteristics and handling requirements;
- AE and Serious Adverse Events (SAE) and its reports;
- ISF;
- CRF;
- Source documents;
- Delegation Log;
- Central Laboratory;
- Pharmacy conditions;
- Monitoring Requirements;
- Complementary Exams;

It was also an opportunity for the research team to ask questions concerning the trial. After the presentation was concluded, I provided help to my coordinator colleagues and to the CRA, by organizing and archiving the study documents, seeing if the delegation log was properly

signed, requesting signatures and curricula of some members of the research team that could not attend the site initiation visit and collecting some equipment certificates.

- **Preparing Study Visits**

When the clinical trials were ongoing, it was the study coordinator's responsibility to conduct them according to the timelines and procedures described in the protocol. Each participant's dossier had a schedule with the time window for each visit; the study coordinator's function was to schedule these visits according to the participants' and study team members' availability. However, it was important that the period established by the sponsor for each visit was not exceeded, so as to avoid a protocol deviation.

A good preparation of the study visits was essential because that decreased the probability of error, and the anxiety of the team, while increasing self-reliance. This preparation included reading the protocol procedures corresponding to the specific visit for that participant, as well as the preparation of the material that should be available for that visit. All necessary information was in the protocol, frequently presented in tables.

Most visits required a diversified evaluation, such as a clinical evaluation, vital signs' assessment, psychological assessments, samples' collection, electrocardiogram and quality of life questionnaires. Obviously, there were several professionals involved in one single visit and because of that, a previous organisation is fundamental. 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 signs form and pharmacy prescription forms. I also labelled the laboratory tubes, when necessary.

Some important topics will be explained below in order to better understand the differences between study visits.

First visit

The presentation and explanation of the ICF mark significantly the first visit to the clinical site. The PI delivers a copy of this form to the participant, giving him or her the opportunity to read and think about the study. After that, another contact is scheduled to know about the patient's decision and discuss any doubts that may exist. If the patient agrees to participate in the study, the screening procedures are initiated.

Screening Visit and Baseline/Randomisation Visit

A screening visit happens if the patient agrees to participate in the study. In this type of visit, I supported the investigator in any doubt about the ICF, the protocol and informed the patients about our availability in helping them with any situation related to the clinical trial.

The screening visit was the first step for the participation of the patient in the study. Between this visit and the baseline visit several complementary exams were frequently required in order to confirm if the individual was apt to participate. I had to schedule these exams, organise the transportation and inform the participants. After that, if the exams' results were favourable, I scheduled a baseline/randomisation visit.

In the baseline/randomisation visit, some auxiliary evaluations were performed and the IMP was delivered. It was explained to the participants and to their caregivers how to take the IMP and any special precautions to take. Sometimes the patient did not meet the eligibility criteria to enter the study and, in these cases, the participants were deemed as a screening failure. During my internship, I witnessed several screening failures, frequently with patients that had to carry out psychological scales and were in an early stage of the disease. The research team rescreened some of these patients once the conditions that prevented them from participating.

Regular Visits

During my internship, I was responsible for contacting the study participants a few days before the scheduled day for the visit, in order to guarantee their attendance and ensure they had not experienced an ADR between visits.

Generally, to prepare a regular visit I looked at the tables presented in the protocol, verified which procedures had to be performed and collected the necessary documents from the cabinet, organising them. I prepared the patient´s medical record, IVRS/IWRS worksheets, laboratory kits and requisition forms, vital signs record form, the worksheet to schedule the complementary exams, and the requisition to order dry ice, when applicable.

Some clinical trials had specific worksheets for each visit, with the procedures to be performed. We registered the data collected during the visit in these worksheets. These checklists were usually delivered by the sponsor/CRO and I considered them important for our internal organization and assurance of correct data collection. In those cases where the checklists were not provided, I created them, in order to organize all the procedures and tasks of clinical trials in which I was involved.

In some studies, patients took the medication at home and when they came to the clinical site, I received the IMP and returned it to the hospital pharmacy, but always after checking it and verifying the patient's treatment compliance. I also checked the medication that the participant would need between the site visits and requested it to the pharmacy. When a collection of biological samples, vital signs, electrocardiogram and administration of psychological scales were necessary, I provided support and performed some of these procedures.

ICF amendments throughout the study were common, due to information being changed, added or removed from the protocol. Even if these were small changes, the study coordinator was required to instruct the investigator to sign and date a new ICF and the participants were informed about the changes.

Sometimes the participants suffered AEs. In these cases, a more detailed assessment was required and only then did the investigator decide what should be done. In certain cases, when the condition was doubtful, the PI contacted the CRA to discuss the condition with the sponsor. When the health situation was not favourable to allow the patient to continue in the clinical trial, the PI advised the patient to leave the study, and an early termination was performed. I witnessed one early termination situation, where I was responsible for contacting the participant in order to ask if he wanted to continue the study but he refused it. Due to this, it was considered an early termination and the patient later performed a follow-up visit.

The completion of IVRS or IWRS allowed to conclude the process concerning the prescription of medication. I performed these under the supervision of the site study coordinators. In visits when the IMP was dispensed, I filled the pharmacy prescription form with the medication lot number, signed and dated by the investigator, and then I sent it to the pharmacy through e-mail. When the IMP arrived at the Department of Neurology, the investigator registered the lot number and the identification number on the subject's process. The IMP was delivered to the patient, and the patient received instructions on how to take it. I also explained the details on the next appointment. In some clinical trials, the medication was only administered at the clinical site through infusion.

After all this process, I verified the patient's expenses and carried out the necessary reimbursements.

After the Visit

After the visit, I reviewed all source documents to ensure that all necessary data were collected and were consistent. I introduced the data in the eCRF. Usually, after this procedure, some queries would appear. Prompt resolution of queries was of maximum importance. The simple ones, like data entry errors, were quick to solve, but the ones that were more complex, like the ones related to inconsistences or incoherencies required a team effort amongst investigators and coordinators to be solved.

If an electrocardiogram was done on a given visit, I would send it to the central laboratory for evaluation. I also verified the SAEs and AEs reports and their respective follow-up. Finally, I archived all the documents and used material in the patient's folder in their respective division of the archive room.

- **Monitoring Visits**

The role of the monitor/CRA is critical for the development of the clinical trial. The monitoring visits are visits that the CRA undertakes at the study site to verify the compliance of the collected data with the study's protocol. Firstly, the monitor/CRA contacts the site (via email or phone) to schedule the visit according to the PI's, co-investigators' and study coordinators' availability. After finding a compatible date, the monitor/CRA went to the centre. Days before the visit, I organized the participants' dossiers, solved queries and reviewed pending issues from the last monitoring visits. When the monitor arrived at the centre, he or she verified all source documents and I helped him or her to read the patients' records and to find specific information. After this, the monitor met the PI and the study coordinators to clarify further doubts.

- **Close-out Visit**

The close-out visit occur after the last patient visit, when the site has already finished the recruitment period and all patients have completed their last visit. All CRFs and documents must be updated and completed with no queries left open. At this moment, the sponsor can close out the clinical trial at the site. I helped the group to answer queries and update some documents. After that, the essential study documents stayed at the site until further instructions from the sponsor. Usually, the next step was the archiving of the clinical trial documents in the archive department of the HSM-CHLN.

- **Archiving documents**

I also assisted in the organization of the physical space of the unit. After the clinical trials' close-out visits, the documents should be archived during at least 15 years after the end of the study, according to national legislation (15). After the sponsor's authorisation and after contacting the central archive of the HSM-CHLN, I helped to store the essential documentation in boxes and to take them to the central hospital's archive. The boxes should be properly identified in case they need to be consulted posteriorly. To facilitate the identification of the boxes, we made labels with the name and number of clinical trial protocol, PI identification, sponsor identification, and when applicable, the CRO's address and contact.

- **Other activities**

During my internship in Clinical Trials sub-unit I also performed other activities. I regularly contacted the study monitor in order to clarify any doubts or how to procedure in particular situation or how to resolve some queries. This contact happened through e-mail, telephone and sometimes face-to-face. Because the CRA was the bridge between the clinical centre and the sponsor, he/she was always close to the research group. This strict communication avoided protocol violations. I also had to be in touch with external clinicians, central group and company of transport. This situation was due to the fact that sponsors/CRO made contracts with other entities to perform the complementary exams.

I also archived documents and performed some activities of quality management. Specifically, in order to ensure the proper conditions of the material I verified the validation date of the material used, such as laboratory kits, and if anything was missing.

To ensure a good conduction of the patients' visits, every Friday the study coordinator organised a timetable with all the visits and important events in the unit and sent this document by e-mail to all members involved, like PIs, laboratory technician, pharmacists, ratters, nurses and other team elements.

Clinical trials sub-unit is placed in Neurology department. Therefore, we frequently collaborate in the packaging and shipping of blood samples that came from the Day Hospital. We were going to get the patients' samples properly identified, we pack them in adequate kits and we called the carrier. Complementary to the main activities I usually did the download of the temperature recorded by freezer temperature logs once a week.

2.2. Generic Training

The following sections describe the activities that I consider more generic, each divided by the sub-units I have worked at.

2.2.1. Activities at the Biostatistics and Methodological Sub-unit

For the first two months of my internship, I worked at the Biostatistics and Methodological sub-unit, where I mainly performed medical writing and clinical data management activities. During the first two weeks, I was introduced to the activities that were performed at the LCP, by reading some dossiers with the reports of the scientific projects submitted to national and international institutions. The principal research areas are neurodegenerative pathologies, with studies about pharmacologic and non-pharmacologic therapeutic approaches. Besides the statistical analysis of clinical data, the sub-unit gives support in writing tasks for the submission of applications for funding and in the final editing of manuscripts that are submitted for publication. With the end of this introductory period, I was given the chance to work in several medical writing and clinical data management projects.

Medical writing is a set of activities with the purpose of communicating with rigor new scientific information to different audiences. These activities require clear understanding of the medical concepts and ideas, and an ability to present the data and their interpretation in a way the target audience will understand. This implies the use of an appropriate language and adaptation of technical terms' use to the audience. Moreover, the writing needs to meet the specific requirements of the different types of documents, and it is now an important function in the pharmaceutical industry (55, 56).

2.2.1.1. Medical Writing and Data Management

To contextualize my activities as medical writer and data manager, I will provide in the following paragraphs a brief overview of what is a systematic review and a meta-analysis. Then, I will detail the activities that I performed in this context, since all the projects I was involved in at this sub-unit were systematic reviews and meta-analysis, except the first one.

Systematic reviews and meta-analysis are a key element of the current evidence-based healthcare, followed by RCTs, in terms of "ranking of evidence"(57). Evidence-based medicine integrates individual clinical expertise with the best available external clinical evidence from systematic research (58). A systematic review is a type of review article. A review article can be defined as a scientific text that results from a constructive analysis of previously published

literature or data about a specific topic (58). This results in a stand-alone publication, structured with a title, an informative abstract; an introduction; a chapter with material, methods and results; a discussion; a conclusion and the references (57).

A review earns the adjective systematic if it is based on some essential premises. It results of a clear, previously formulated research question, followed by the identification, selection and assessment of the relevant literature's quality and a synthesis of all the relevant articles on a given topic (57). Thus, the result of a systematic review is a summary of the best available evidence relevant to the research question that will allow it to be answered (57). This summary of the information is performed by use of explicit procedures, namely strict statistical analysis. Frequently, a systematic review includes a meta-analysis component, where statistical techniques are used to synthesize the data of all included studies into a single quantitative estimate or summary effect size. These are particularly helpful for 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. Systematic reviews have a broader and more explicit approach that allows the minimization of bias, possessing many advantages over traditional reviews (57, 58).

2.2.1.1.1. Cardiology projects

In October, I met a cardiologist intern and PhD student that collaborated with the LCP. He suggested that I collaborated with him in some of his research projects, related to cardiology topics.

Despite most of this physician's publications being systematic reviews and meta-analysis, the first project that he proposed to me was retrospective, observational, pharmacovigilance study. The objective was to assess all oral anticoagulant-related spontaneous notifications of AEs in the last 5 years reported to the Portuguese Pharmacovigilance Database. Initially, he presented a pharmacovigilance database with spontaneous reports of ADR related to the use of new oral anticoagulants (NOACs) available on the Portuguese market. INFARMED provided this database and because I was not an expert in cardiology and did not have practical experience in pharmacovigilance, the investigator started with a contextualization of the current prescription of NOACs in Portugal and the importance of the use of these drugs in the treatment of certain prothrombotic conditions. I was responsible for the classification of each ADR present in the database and for its analysis according to the Preferred Term, the System Organ Class and suspected anticoagulant drug. For this classification, I had to learn about the use of the Medical

Dictionary for Regulatory Activities (MedDRa), an important tool in pharmacovigilance and drug safety monitoring. Thrombotic and bleeding events are relevant outcomes in patients under vitamin K antagonists or NOAC treatment. Thus, they are distributed across the different System Organ Class and consequently along broad terms of the Standardised MedDRA Queries.

After data management, I built several tables and graphics for the presentation of results and discussed them with the physician. I contributed to the writing of every section of the article, with important contributions and orientations of this professional, especially in the discussion section. This paper was submitted to a national publication of the clinical area with the title: *Adverse drug reactions with oral anticoagulants in Portugal: data from the national pharmacovigilance database of spontaneous reports*.

After this, I collaborate again with this cardiologist in the execution of a systematic review and meta-analysis about the security of NOACs. The underlying assumption of the study was the assessment of the coronary risks of NOACs based on findings from placebo-controlled trials. We performed a meta-analysis that included results from both interventional trials and observational studies. Although I had an active role only on the screening of some observational studies that were included, in data extraction and in the presentation of results through several tables, this collaboration was important to me because it was my first contact with the real execution of a systematic review and meta-analysis. Until then, I knew the steps necessary for the execution of a systematic review, but I never had to put them in practice.

The physician explained me some important concepts, including the interpretation of the data that was collected and statistically analysed through Review Manager (RevMan®), a software for conducting meta-analysis. The article, entitled: *"Safety of non-vitamin K antagonist oral anticoagulants - coronary risks"*, was accepted on March of 2016 for publication in the journal Expert Opinion on Drug Safety (Impact factor – 2.911).

At the same time, I collaborated in other cardiology systematic review with meta-analysis about the use of NOACs in elderly patients with atrial fibrillation. It was important to study the use of certain medications, like NOACs, in special populations. We reviewed and quantified, through the meta-analysis of RCTs, the efficacy and safety parameters of NOACs in the elderly population, in comparison with their impact in younger patients. We searched in MEDLINE, Cochrane Library, SciELO collection and Web of Science databases. Two authors reviewed the trials and calculated the risk ratios using a random effects model. I collaborated in data extraction

and in the writing of some parts of the article. I also participated in the preparation of tables for the presentation of results. The article, with the title "*Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: a systematic review with meta-analysis*", was submitted.

When I finished my internship at Statistics and Methodological sub-unit, I continued to collaborate with this cardiologist on his projects. The following project was a systematic review and meta-analysis with the aim of evaluating the risk of cardiovascular events related to coffee consumption in patients with previous myocardial infarction. The investigator proposed the topic and it interested me very much because I always thought about the cardiovascular consequences of coffee consumption and this was an opportunity to find some published evidence about this topic. It also seemed interesting to study a beverage consumed worldwide and its association with a medical condition that causes several comorbidities. After this, my colleague and I established a protocol with the steps to perform the systematic review - PICOS. With the help of RevMan guidance, we defined our objectives and all the topics necessary to do this paper. After establishing the research protocol, we discussed it with the physician and defined a research strategy to be used in the PubMed/MEDLINE database. After researching all available information about the topic, we performed the screening of the articles, taking into account our final objectives. Using Covidence, we imported the citations from MEDLINE and screened them, independently. Posteriorly, we extracted the full texts of the selected articles and performed a full text review in the same platform. Covidence is a web-based software platform recommended by Cochrane that improves the production of systematic reviews (59). After we screened the articles, we extracted the study characteristics and other study data, building the tables for the presentation of results. After a critical analysis, data were exported into the relevant RevMan tables or spreadsheets, so the meta-analysis could be performed. I also collaborated in the writing of some parts of the paper, like the introduction, the materials and methods and the results.

2.2.1.1.2. Clinical Pharmacology Project

Two weeks after I had started my internship at the Statistical and Methodological sub-unit, Professor Joaquim Ferreira challenged me to work with him in a subject that he wanted to explore – Clinical Pharmacology teaching. Because our laboratory was clearly associated to this discipline and most of the professionals that work at the LCP teach Clinical Pharmacology and

Therapeutics to FMUL students, it seemed to be an important issue to explore. Afterwards, we discussed the objectives of our project and the better approach to perform it.

Professor Joaquim Ferreira was interested in doing a systematic review of all the available evidence about the teaching of clinical pharmacology in medical schools all over the world, namely a presentation and examination of the different curricula for undergraduate students, the years when the discipline was taught, the duration of the courses, the teaching methodologies used, the core skills and the programs' contents, if these were mandatory or elective courses, if a student formulary was done, if the curricula included classes with patient interaction and, finally, the methodologies for the assessment of the students' performance. Professor Joaquim Ferreira and I established a search strategy that I applied to the Pubmed/MEDLINE database. I imported the available citations from PubMed to a reference management software (EndNote), eliminated duplicates and screened the articles. After I had the bibliography library, I started to extract the data from papers and organizing it in an Excel sheet. It was a difficult task because the available information was heterogeneous, even inside the same country and the published data were presented in different ways. Because there was not a standard presentation of the data, I had to adapt my methodologies for its collection as I read the articles. During this time, Professor Joaquim Ferreira gave me tips to better perform data extraction and management. After a consensus about the available information, I was responsible for presenting the results (tables and graphics) and writing the article, with the supervision and revision of Professor Joaquim Ferreira.

2.2.2. Activities in the Outcomes Sub-unit

During about one month and a half, I had the opportunity to collaborate in various activities of the Outcomes sub-unit, whose principal responsible is a MD, PhD, paediatrician at the HSM-CHLN and a member of the LCP.

2.2.2.1. Observational Study Monitoring - ALFABETO

The main project I participated in was *ALFABETO - ALto Fluxo – Antever na Bronquiolite a Eficácia Terapêutica e Outcomes*. ALFABETO was an observational, pilot, prospective study. Its primary objective was to identify, in an exploratory way, the demographic, clinical and physiological prognostic factors responsible for the success/failure of high flow nasal cannula oxygen therapy in paediatric acute bronchiolitis. When I started to collaborate with the PI, this multicentre study had three clinical centres with all documents approved and ready to receive the

study – HSM-CHLN; Hospital Beatriz Ângelo and Hospital Fernando da Fonseca. However, Hospital Garcia de Orta was also interested in taking part in this project. Thereupon, my first tasks were to update and to adjust the study orientation documents, the ICF, study protocol, CRF and the archiving dossiers in order to provide all the necessary tools for the participation of Hospital Garcia de Orta. When all legal authorizations were obtained from the site, the study was ready to be implemented and the patients could start to be recruited in all centres. I was responsible for the project management activities, always following GCP and the procedures described in the study protocol.

ALFABETO was a pilot study and the centres involved did not have enough experience in high flow oxygen therapy. Thus, I prepared and updated some educational material for the health care professionals to start becoming familiar with the equipment and study procedures. This material included equipment orientation documents, USB drives with tutorials and study contents, and dossiers with the study information for each centre.

When the first participants that were eligible for the study were included and received the high flow oxygen therapy, I started to perform study-monitoring activities. I optimized and adapted the previously elaborated study databases. I also received the paper CRFs from the centres and entered the information in the databases. At that time, as the study monitor, I was also checking the validity of the available data and making queries, in order to improve the quality of the entered data and to solve some mistakes in the filling of the CRF. During this process, I periodically wrote a newsletter to make the team aware of the status of the study. These newsletters included some important topics that the investigator and I considered important to clarify to the other study elements. These points could be some recurrent queries that I detected in the CRF or some procedures that could require special attention and standardization in order to increase data quality. I also had the responsibility to alert a co-investigator of our centre for the parents' contact, as described per protocol. It was also my function to collaborate with the PI in raising awareness with the research teams and to contact with other centres in order to clarify some doubts about the filling of the CRF. During this time, I also did some logistic tasks, such as counting, organizing and registering the study material available at the Department of Paediatrics of the HSM.

2.2.2.2. Academic Project – Outcomes in Paediatrics

In parallel with the project management activities of the previous observational study, I collaborated in an academic project whose supervisor was the previously mentioned investigator.

This project, with a focus on Paediatric investigation, was the final dissertation of a FMUL medical student.

It was a systematic review of the scientific articles about acute diseases in paediatrics, namely, acute bronchiolitis. This review had the primary objectives of assessing the prevalence of exclusion criteria in clinical trials of paediatric acute conditions, evaluate, and describe the hospital related outcomes. I participated in the discussion and in the establishment of a PICOS for this project, according with its main objectives. Afterwards, with the help of another investigator, we established a search strategy based on the eligibility criteria of the study – RCT; paediatric populations (<18 years); the existence of a chronic condition (acute bronchiolitis-as defined by the study authors); treatment and in any language. After we had created the search strategy, we tested it on the Cochrane database to search for systematic reviews. These systematic reviews were used as the primary source of information. Posteriorly, we created a list of the clinical trials that were included on these systematic reviews. After this systematization of the information, it was necessary to screen the systematic reviews and the clinical trials that fit our purpose. We created two Endnote libraries to archive our search: one for the systematic reviews and another for the clinical trials.

I was responsible for the elaboration of a data collection key, an instrument that could be used by three independent investigators. This helps by standardizing the data collection for the studies' and, consequently, the project's quality. It helped to analyse the functionality of the Excel sheet previously elaborated. Then, we extracted all the important data according to our objectives. These data, presented in tables, were following analysed and graphics and tables were created to show our results. I also collaborated in this process. This systematic review, entitled: *"Children with Chronic Diseases in Pediatric Clinical Trials",* was present to FMUL as the final project of the Master's Degree in Medicine. After I finished my internship at the Outcomes Sub-unit, I continued to work in the elaboration of this systematic review.

2.2.3. Activities in the Safety and Drug Utilisation Research Sub-Unit

When competent authorities approve a drug, it can be commercialised. However, a continuous verification of its effects in the general population is necessary. According to the World Health Organization (WHO), pharmacovigilance is the science relating to the detection, assessment, understanding and prevention of the adverse effects of medicines.

Internationally, the Pharmacovigilance system is connected to the Vigibase, a worldwide database of ADRs, which is continuously updated and maintained by the Uppsala Monitoring

Centre, and the EMA database, the Eudravigilance Data Base Management System, where ADRs related to medicinal products marketed in the EU are recorded.

Since 2000, the Pharmacovigilance system gained a new structure, with the creation of regional centres responsible for collecting spontaneous ADR reports from healthcare professionals. Patient spontaneous reporting has also been available in Portugal since 2012, when the new pharmacovigilance legislation came into force. This has increased the number of spontaneous ADR notifications (60). At the moment, there are four regional pharmacovigilance units. These centres cover the entire region of Portugal, playing a key role in encouraging the reporting of ADRs, involving universities to promote their scientific and technical expertise and in spreading the system (61).

My collaboration at the UFLVT started in January and lasted two months. The first two weeks were an introductory phase to Pharmacovigilance concepts and procedures. During the rest of the time, I developed activities related to drug safety monitoring.

The introductory phase started with a brief oral explanation by a Quality Manager and Pharmacovigilance Technician about the main purposes of the UFLVT and the activities developed to reach their objectives. After that, I read some related scientific literature and guidance, for instance, the book “Farmacovigilância em Portugal” (62). I also learnt about the context of pharmacovigilance in the current regulatory framework by reading the Good Pharmacovigilance Practices guidelines. I also had the opportunity to get to know the Quality Management System (QMS) and access the QMS documentation (quality manual, processes, operational procedures, work instructions, document templates and records). The QMS was implemented in the UFLVT three years ago, in order to harmonize the procedures, with the final objective of minimizing errors and increasing the quality of results. I read other dossiers that allowed me to understand the structure of the UFLVT and the functions of each collaborator, as well as the interaction with the competent authority-INFARMED.

After the initial training, I was able to collaborate in the daily activities of the UFLVT. The daily responsibilities of the unit included the collection, management, and assessment of medicines’ safety data. This assessment could result in the detection of abnormalities in the data that should be reported, through safety warning signs based on the evidence of ADRs. I started to learn how to receive and validate notifications that came through different ways. When the unit received a spontaneous ADR notification, it could arrive by e-mail, telephone, fax or mail. UFLVT had specific formularies to collect the notification data, depending on the entity that made the notification. Sometimes I filled these sheets with information received by telephone. A suspected

ADR may be notified to the Marketing Authorisation Holder of the suspected drug, directly to INFARMED, or to the Regional Unit of the notifier's area of activity or residence. The notification process became simpler because users and health professionals started to submit their ADR notifications through electronic submission in Portal RAM.

One of my first tasks at the UFLVT was to learn the four minimum requisites to validate an ADR notification: identification about the notifier; identification about the patient; the suspected active substance; and a signal or symptom of an ADR. If the report was considered valid, the notification was assessed. After this validation, the notification was dated, signed and a number code was assigned. In order to confirm the existence of the notifier and to collect additional information to write the initial report, the professionals of the UFLVT contacted the notifier directly. I performed these additional information requests, when they were necessary. Subsequently, the notification data, which should be as complete as possible, was inserted in the SVIG and a copy of the original report provided by the notifier was attached. A reply was sent to the notifier confirming data had been received and its report had been accepted. When we entered the notification data in SVIG, we had to search for duplicates, in order to assure that the report did not yet exist in the on-line system. Then, we inserted some relevant demographic information about the patient, as well as his or her pharmacologic and clinical history. Data about the notifier, the ADR and the suspected drug were also necessary. While the notifications were being processed, it was necessary to check if the reported reaction was already described in the Summary of Product Characteristics of the suspected drug or in the available literature, because this influenced the final assessment of the notification.

To enter the information characterizing the ADR, it was necessary to use MedDRA, an important, medical terminology tool for ADR classification. This terminology was developed by the ICH, with the goal of standardizing, at the national and international level, the classification system of ADRs. Most of the information was entered in summary form, but this can be supplemented with narrative information, including notifier's comments. The entry of data on SVIG was communicated to the Pharmacovigilance department of INFARMED and a specific code for the notification was generated. All of the cases reported nationally are filed in SVIG's national database. Later, this information is shared with the EMA and the WHO, allowing its analysis in broader contexts.

The medical coordinator of the unit, neurologist and member of the Committee for Medicinal Products for Human Use - EMA, assessed the notifications, in order to assign the proper causality category, which was posteriorly added to the notification's SVIG record. According to

the Uppsala Monitoring Centre, the causality of an ADR can be classified as follows: certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable (63). During my internship, I prepared several documents with all the notification data, in order for the medical director to attribute the causality.

Afterwards, a summary report about the case, as well as all the important information and details necessary to understand it, was written. This report was attached to the original notification and archived in the UFLVT. During my internship, I frequently did narratives of some notifications that were posteriorly verified by the UFLVT experienced collaborators.

Depending on the outcome and severity of the ADR, the notifier can be contacted by the UFLVT in order to update and follow-up the case until the case is considered finalised. The notifier was afterwards informed about the causality classification attributed to the notified suspect ADR, and if any decision related to the medicine was made based on the spontaneous notification. A warning sign, resulting from a quality or efficacy problem detected in the notification, may be generated. These cases had to be assessed by the clinical coordinator and, after a decision had been made, a report was sent to the Direction of Inspection and Licensing, so that the case could be followed.

In the last weeks of my internship at the UFLVT, I attended the first meetings about the implementation of a clinical trials pharmacovigilance system. I did some research in the guidelines and legislation currently in force. This type of systems must be in place to enable the identification, recording, reporting and analysis of safety information so that any safety signals that arise during a trial are quickly identified and acted upon. I also took part in a meeting with the UFLVT professionals for the discussion of some important aspects in UFLVT's activities that should be improved and of the achievement of UFLVT's objectives, as well as for the planning of future projects, strategies and educational courses.

By the end of the internship, I was able to perform autonomously some of these daily activities of the unit. I could verify that every person in this sub-unit was responsible for a separate set of tasks, in sequence, with the workflow resembling an assembly line. First, the ADR notification was received. A time limit was set on the calendar for completing the coding, recording the AE, and conducting the follow-up process.

2.2.4. Other Activities

- **Good Clinical Practices Course**

On December 4th, 2015, I attended the GCP course organized by the LCP. Because the complying with the GCPs is essential to perform clinical research with quality and rigor, the knowledge of GCP concepts and practical rules is mandatory for everyone who wants to do investigation with human beings. The LCP professionals, with extensive background in these topics, presented the several themes discussed during the course. It started with an introduction to the GCP principles, followed by a regulatory framework. The importance and content of the study protocol were also covered, as well as the study's essential documents. The responsibilities and roles of the stakeholders in a clinical study were explained, as well as the pharmacovigilance in clinical trials. Finally, some practical aspects to take into account during the conduction of clinical studies were discussed. During the entire course, the speakers gave space for questions and discussion.

- **Pharmacovigilance Course**

From the 16th to the 19th of November, I attended an intensive course on Pharmacovigilance, in the facilities of the HSM-CHLN and organized by the UFLVT. The course provided an overview on the different mechanisms of ADR spontaneous notification, the importance of performing risk-benefit assessments, pharmacoepidemiologic studies and causality assessment of ADR. The course also provided an overview of the National Pharmacovigilance System. The course then gave a rundown of the most common AEs notified for the main anatomical groups.

- **Wednesday Meetings**

Every two weeks, on Wednesday afternoons, a meeting on the LCP was held with all members of the team. In these meetings, projects in areas like clinical pharmacology, cardiology and neurology were presented. The majority of these presentations were performed by LCP's members and were about projects that they were working on. This helped the team members get to know what everyone was working on, discuss the project or an idea for a project, provide feedback and opinions, or just show the results of their labour.

- **Journal Club**

The Journal Club meetings happened every Wednesday mornings and took place in the Neurology Department, where the Clinical Trials sub-unit is located. These meetings were composed by neurologists and by other health professionals that collaborate with the LCP and the Neurology department of the HSM-CHLN. Each week, one member of the team was assigned to bring a recent article in the field of neurology and neurosciences. The article was explained to the rest of the team, with a description of the methodologies and the study's findings. After that, there was space for discussion, usually about the design of the study, the potential therapeutic applications of the findings, the pertinence of the article on the actual reality of medicine, amongst other relevant topics. Besides the presentation of recent scientific papers, these meetings also included video sessions, with the presentation of some clinical cases related to specific neurologic conditions, which were important to share with other health professionals. In these meetings, the research projects of some team members were also presented.

- **Internal Workshop: Assessment of Risk of Bias Tool**

The assessment risk of bias tool is an important instrument used to evaluate the quality of a systematic review and meta-analysis. Since part of my internship at the LCP was spent collaborating in the execution of systematic reviews and meta-analysis, I participated in a workshop presented by a member of the Cochrane group and LCP, that was focused on the explanation of this recommended approach for assessing risk of bias in studies included in Cochrane reviews. Two parts compose this tool. Each domain in the tool includes one or more specific entries in a 'risk of bias' table. Within each entry, the first part of the tool describes what was reported to have happened in the study, in sufficient detail to support a judgement about the risk of bias. The second part of the tool assesses the risk of bias for that topic. This is achieved by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. In the end, a quality score is attributed to the systematic review.

- **Data Entry**

I collaborated with a LCP member in the process of data entry. This data corresponded to results from a validation study of a scale for Parkinson's disease - Movement Disorder Society-Unified Parkinson's Disease Rating Scale. I entered the data from the CRFs into a computer system database, in this case, Excel. It was indispensable to confirm the correct introduction of results with the help of independent investigators.

3. Discussion

During this training, I had the opportunity to understand more about the practice of clinical research not only through the support given in the conduction of clinical trials and observational studies, but also through the participation in several medical writing projects and in pharmacovigilance activities, thereby contributing to further scientific progress. These ten months were full of experiences, constant knowledge and hard work. Little things and situations that, overall, enriched my training and improved some personal and professional skills followed the major projects and activities that I previously described.

A multidisciplinary team collaborates in the various sub-units that compose the LCP, the host institution. The projects developed allowed the exploration of several approaches related to clinical research and clinical pharmacology. Thus, the opportunity of doing an internship at the LCP was clearly a very enriching experience in these areas. I had the opportunity to work in these different research departments, do several activities, learn with senior professionals and be in contact with patients. Although I have been mainly involved in the coordination activities of several clinical studies, I also gave support to physicians in their academic research projects, developing and preparing papers about current themes in clinical research, monitoring an observational study in paediatrics and following the daily activities of a pharmacovigilance regional unit.

The Clinical Trials sub-unit is a very well organised centre composed of experienced and qualified professionals and all the procedures are performed in compliance with protocol requirements, ethical guidances and regulatory guidelines. During my internship, I realized how difficult it is to conduct a clinical study, since it involves several health professionals with particular functions. It is of maximum importance to maintain everyone focused, aware of each other's roles and of the study objectives. I learnt about the several hurdles that have to be overcome during the conduction of a clinical trial and which frequently discouraged team members. However, it was gratifying to see the resilience and the constant search for solutions, to solve any problems that arose. This strategy had the intention to produce quality data and transform the Clinical Trials sub-unit into a reference centre.

My experience as study coordinator trainee made me realize the key role of this class of health professionals in clinical trials. From the beginning to the end of the clinical trial, the study coordinator manages the operational aspects of medical research studies, being responsible for

ensuring that the research team strictly follows the protocol procedures, which requires high organizational skills. Entering data on the study's CRF platforms, as well as assisting the monitors/CRA, are also responsibilities of the study coordinator. Since we contacted directly with study participants, it was necessary to develop communication skills, in order to be able to manage their anxieties and expectations, but at the same time to be efficient and scientifically rigorous in the transmission of information to investigators, monitors and other team members. This contact and consequent collaboration between study coordinator and all research team members happens during the study submission and coordination. I had to adapt my discourse to the patients, according to scientific requirements. Initially, I had some difficulties, but with time, I learned how to deal with them. I had to learn what information I could transmit and how I could do it. Another point that I needed to improve was how to manage my feelings. Sometimes it was difficult to maintain the distance between me, as a health professional, and the patient. Over time, I developed strategies to overcome this difficulty.

When I started my training at the Clinical Trials sub-unit, I had some difficulties. It was necessary to understand the sequence of procedures and tasks needed for each study that I was allocated to; in organizing the study visits according to the timelines and the patients and professional's availability; in identifying the research group of all studies; in applying some particular procedures and in providing certain materials. Despite all studies' documentation being organized in the cabinets and despite me having some theoretical knowledge obtained during the first year of the Master's degree, there was a big amount of new information, which I had to adapt to. However, when I was not sure of something, I always asked for help in order to clarify these doubts. Because we were dealing with people's lives, it was fundamental to be truly sure of all the steps to take. Then, when I had understood the activities and got to the point where I could play an active role in the centre, I tried to improve the activities learned.

The Clinical Trials sub-unit participates in different clinical trials and observational studies. Most of them are phase II and phase III clinical trials. This is in line with the overall Portuguese trend, as shown by INFARMED's statistics (44, 46).

Due to the high number of phase II and III ongoing clinical trials, I contacted with a wide range of procedures to follow. In addition, the several types of visits in each study allowed me to manage several facilities and information, as well as to work closely with the different team members. Thus, during my training, every day was a challenge. I had the opportunity to contact with new things constantly and I learned throughout the whole period. It forced me to grow as a person and as a professional, improving my responsibility, time management, self-confidence and

teamwork skills. The multidisciplinary specialist approach allowed me to contact with neurologists, psychologists, study coordinators, monitors/CRAs, statisticians, laboratory technicians, nurses, pharmacists and other professionals that, ensured the conduction of the studies. They were always available to share their experience and helped me with their solid background in clinical research. This context also provided me with the advantage of increasing my network of working contacts.

The clinical site received protocol amendments several times, and these corresponded to updates to the procedures of the clinical trials, implemented as result of the studies' course or of legislative changes. These updates reflect the quickness with which changes happen in the clinical research world and how unexpectedly events may occur, even if we work to minimize them.

In 2016, one man died and four others fell ill during a drug safety study in France (64). The case, involving the Portuguese pharmaceutical company Bial, brought to the agenda the issue of clinical research. Biotrial, the company's French CRO partner, was testing a compound called BIA 10-2474, developed by Bial as a candidate drug for a range of diseases (64). Despite the expert panel's final report, stating that the death of one of the participants in this phase I clinical trial was most likely caused by the drug's toxicity, several inaccuracies, translation mistakes, and transcription errors in the documents submitted by the sponsor were also revealed. This occurrence alerted the scientific and medical communities to the need for stricter regulation and for a higher accuracy in the conduction of clinical trials - "The seriousness of the accident at Rennes justifies changes to the regulations and to international best practices" (65). This event occurred shortly before I started my training in coordination, which made me think about the responsibility of performing all the clinical trial activities and the duty of complying with the procedures according to the protocol and the legislation in force. The need for a set of universal, stringently enforced guidelines has been reinforced. It was also suggested the creation of an international expert panel to continually review best practices and devise protocols in line with the most up-to-date information. Furthermore, the official bodies should supervise more the trials they approve closely. Greater transparency must also apply to regulators.

The diversified composition of the research group and the direct contact with the stakeholders of a clinical research unit allowed me to learn a lot and improve my communication competencies, organisational skills and the knowledge previously acquired in the Bachelor's degree and in the first year of my Master's course. It was possible to apply and complement concepts learned in the classroom, to learn more due a new perspective (on the job) and to get prepared for the real world of clinical research.

During almost all my internship, I maintained data management and medical writing activities, as result of collaborations in diverse academic projects. These experiences gave me the opportunity to improve my communication and research skills. I was also able to complement my experience and expand my knowledge in areas like cardiology, clinical pharmacology and paediatrics. I had to study each topic carefully, to be able to write on a given subject with confidence. Regarding clinical pharmacology, data extraction was initially a difficulty, because I had to extract qualitative data that was quite heterogeneous. Presenting results with this data was a challenge for me, but at the same time, I developed the ability to synthesize and group information. I learned to search in Pubmed/MEDLINE and to construct systematic search strategies to find articles on specific themes. Furthermore, I improved my critical analysis skills and learned to write a scientific paper rigorously. I also learned how to create an Endnote library and to manage my references. This was a very promising learning because it seems to me that it will be very useful in the future. To present the statistical results, I learned to manage the SPSS software with the help of a statistic technician, as well as to discover new tools for data collection in Excel. I learned about some basic concepts on the conduction of a meta-analysis, the type of software that was used, and how to interpret the final result (a forest plot). Regarding the Cochrane Review Group, despite not having directly collaborated with this sub-unit, it also belongs to the LCP structure and I consider the projects developed there to be important. I really enjoyed participating in these projects and the contact with senior professionals with lots of experience and new ideas was a great source of happiness. I could understand that the interest for the practice of evidence-based medicine extended to all professionals working at the unit.

I closely monitored an observational study when I trained in the Outcomes sub-unit. This experience was very enriching, because I faced, for the first time, the practical hurdles of conducting a clinical study. This academic project, ALFABETO, was interesting, because I started to collaborate on this project when the first child was recruited. When I received the first CRF to update the database, I was faced with some errors and missing data, which in the end would decrease the quality of results. Therefore, I had to generate queries and contact the investigators in order to clarify the doubts and to give them training about the study and the procedures. Because the target population in this study was a paediatric population, the research team should adopt a special approach in executing the techniques and in data management. The correct training of all the professionals involved was, thus, of maximum importance.

Chronologically, this direct contact with the monitoring world happened before my training in study coordination. I considered that this was a plus in my education, because I

understood early the importance of organizing and updating all study documentation and how important it is that the CRF is correctly filled. When I started my activity as a study coordinator, I was more aware of the importance of communicating with the monitors and of being well trained for the entire study procedures. I think my participation as ALFABETO's monitor was positive because I constantly maintained the database updated with new data collected by the investigators and I was also in permanent contact with the PI, giving him my opinion about what needed to be improved for the success of the study.

After I collaborated in ALFABETO's monitoring, I started my internship in UFLVT. A research in the literature made me realize that in the last years, there has been a greater proximity and interaction between notifiers and the system, contributing to their dissemination and for the progressive increase in the annual notification ratio. This increase was the result of the growing training of the health professionals and due to the implementation of the Good Pharmacovigilance Practices, in 2012. The two months experience at UFLVT was rewarding and surprising. The reception and processing of spontaneous notifications requires not only a critical eye, but also a good sense of organization. Each notification involves a set of little steps with a specific sequence. Initially, it was difficult for me to enter in the unit's dynamic, but with a few days of experience I understood the procedures and I started to analyse each notification critically, using my previous knowledge of some basic concepts acquired in the Bachelor's course and during the first year of the Master's degree. I considered the introductory period a good starting point to recall some concepts and procedures related to Pharmacovigilance and Quality Assurance and its application to the real work of a regional Pharmacovigilance unit integrated in the National Pharmacovigilance System.

When I did not understand any definition or why things were done in a certain way, I always asked UFLVT collaborators for help. I was able to improve my knowledge about some medicines and their particularities. Furthermore, I think I became more aware of the risks inherent to any drug, which require a cautious and continuous assessment of their safety during commercialization. The professionalism of the people who collaborated at the UFLVT was an example for me. All the things that happened during their daily activities, including correspondence with notifiers and with INFARMED, were registered. When there were doubts about any notification or procedures, they quickly discovered the problem and found an efficient solution. I was able to take part in the planning of the pharmacovigilance system for clinical trials, which made me understand the importance of monitoring the drug safety in a period so important and sensible like the clinical trial phases, by reporting all the AEs that may happen

during the course of a clinical study. During the time I stayed at the UFLVT, I was also able to understand the importance of reporting ADRs, the role of this unit in drug safety control, the need for organized and standardized procedures and for quality management.

My Bachelor's Degree in Biomedical Sciences and the first year of the Master's Degree were fundamental during this training. They gave me the principal knowledge to work consistently in a professional environment. Much of the drug legislation, regulatory guidance, ethics documents, anatomy and physiology concepts that I needed to use had already been presented to me throughout my previous education. I had to apply these concepts to be able to develop my activities in clinical research. This previous knowledge allowed me to quickly adapt and to continuously progress throughout the ten months. Obviously, when I arrived at the unit, I had to complement this knowledge with specific instructions and practical tips not taught at school. For example, I had not received training on processing biological samples, performing ECGs and measuring vital signs. These instructions were really important and useful and, in a short time, I was able to integrate the group. Since I worked essentially with neurodegenerative disorders, I had to apply some concepts about the nervous system, acquired in my Bachelor's degree as well. However, in order to understand the objectives and endpoints of the research studies, to help the investigators and enlighten patients' doubts, I needed to learn more about the neurological disorders of the clinical trials I participated in more actively. Namely, I had to search for information about FAP, Parkinson's disease and Huntington's disease.

Regarding my participation as study coordinator, I need to mention my pride in working full-time in two clinical trials about FAP. FAP was an unknown disease for me until then, and it was very interesting to do research work aimed at understanding its particularities and its main manifestations. In TTR02 and in ISIS, I followed the participants in many visits. It was rewarding to have this experience and to see their improvements, when they apparently felt better, but at the same time to have an encouraging word for them when they felt more fragile. It was also interesting to discover that FAP was first described in 1952 in a number of families in Portugal (66). The most common type of FAP affects about 1 in 500 people in some regions of Northern Portugal (66). With the testing of new molecules, such as in these clinical trials, will made possible to slow or stop the nerve damage caused by TTR amyloid deposits and to use the body's natural processes to lower the levels of TTR protein that cause FAP (53).

When I started my internship at the Clinical Trials sub-unit, I had been in the other sub-units for a long period of time, collaborating in medical writing and data management projects and in pharmacovigilance activities. The work dynamic as clinical trials' coordinator was quite

different from the previous ones. Therefore, I had some difficulties adapting to the new work rhythm, but I easily surpassed them over time. Through my activity as a study coordinator, I became more aware of the frequent problems that a Clinical Trials sub-unit can face. I realized that, particularly in clinical studies in neurologic diseases, there were some difficulties in recruiting patients, with high levels of screening failures observed. I verified that this situation was not at all a result of a lack of interest from the research team. Rather, it has been frequently associated to the fact that patients have to undergo strict neuropsychological scales/questionnaires, where they frequently fail the tight inclusion/exclusion criteria and also due to the rigorous design of the study. Development of new medicines in Neurology has also been slow because the therapeutic mechanisms are usually complex and there are significant economic barriers, when compared to other disease areas (14). I consider that the clinical studies in neurodegenerative disorders, like those developed at this unit, are fundamental for the future of our society. According to the WHO, one in four individuals will suffer from a mental disorder at some point in their life. In the USA, it is estimated that, by 2050, Alzheimer's disease alone will affect up to 16 million Americans, more 5.4 million individuals then today, at an annual care cost of US $1.1 trillion (14).

This internship gave me the opportunity to perform some extra activities, which added to my professional skills. The GCP course was an excellent supplement to the knowledge obtained in the Bachelor's and in the Master's degree. It allowed me to tackle, with more confidence, the clinical trial coordination activities of the Clinical Trials sub-unit. The Pharmacovigilance course was a good complement for my internship, since shortly thereafter I started my internship at the Safety and Drug Utilization Research sub-unit. When I started, I was already elucidated about some basic concepts, which facilitated my integration in UFLVT's daily activities. The Wednesday meetings allowed me to understand the importance of rigorous work methodologies and its consequences in the quality of results. I also learned from the wide experience of senior professionals, since the meetings were always quite casual and discussion was encouraged. The Journal club discussions were particularly enlightening, as they highlighted the group's dynamic and different backgrounds, and the prospects that the studies presented could bring to the activities of a research centre. Finally, the Risk of Bias Tool Workshop made me realize that there are no perfect systematic reviews and that it is of maximum importance to identify the weakest points in order to improve in future projects.

4. Conclusion

During my internship at the LCP, I was able to participate in a wide range of activities related to clinical studies coordination, as well as data management, medical writing and pharmacovigilance. Through these activities, I actively collaborated with different work groups, on different projects, and with people with a diverse background and specializations. This allowed me to improve my knowledge, learn with experienced professionals and subsequently expand my working contacts' network.

Despite the majority of the training concerned clinical trial coordination, I had the opportunity to collaborate in other projects. Medical writing and pharmacovigilance are examples of areas that I also worked in during this period. I participated in projects and studies in different neurological disorders – 4 studies in FAP, 2 studies in Huntington's disease, 2 studies in Parkinson's disease, one study in Alzheimer's disease and one study Idiopathic Cervical Dystonia. Two of them were observational studies and the others were phase II and III clinical trials, each for specific indications and with specific requirements. I had to acquire time management and organizational skills in order to plan all activities of a day, taking into account that unexpected situations can happen. At the same time, I acquired technical knowledge about the pathologies and technical procedures. Teamwork is an essential part of the clinical research process. Improving this skill was beneficial for me, because I understood that, in practice, we only achieve our objectives efficiently if we all work for the same purpose, as a team.

As a study coordinator trainee, the participation in the daily activities allowed me to acquire several skills. In this way, every day, I felt the sense of responsibility. A study coordinator must always keep the patient's safety, the GCP and the ethical principles in mind, as well as the need to be compliant with the study protocol. By acting as the bridge between the research staff and the sponsor/CRO, this professional allows both entities to provide feedback on each other's activities.

I enjoyed the interaction with the patients during the internship very much. Each person had a different story to tell. I could closely contact with patients and understand their problems, fears and difficulties. I contacted most of the time with patients with limiting medical conditions. Sometimes it was difficult because I felt the anguish and discouragement of patients. Therefore, in addition to the professional learning, I also grew up personally.

Despite the fact that clinical trial coordination occupied most of internship time, I need to emphasise the monitoring activities. I monitored an observational study in paediatrics that made me realise the importance of this position and its inherent difficulties. I think that, in addition to being a study coordinator, being a monitor is also interesting.

The medical writing projects were another challenge that enabled me to improve my writing and data management skills. I complemented my ability to search for scientific data, organize them and present them in the form of a scientific document. I learned more about systematic reviews and meta-analysis, by contacting with experienced professionals.

The participation in the pharmacovigilance activities of the UFLVT was an excellent opportunity to understand the daily routines of the unit and their relevance. During this training at the UFLVT, I also understood the importance of quality management and internal organization for the success of an institution.

I enjoyed the training due to the good structure of the host institution, the teamwork spirit, the type of activities developed and the contact with the patients. This experience of ten months was very rewarding to me because I felt that, directly or indirectly, I was contributing to a positive impact in the life of other people. I started to perform clinical research activities and had the opportunity to collaborate with a multidisciplinary team with professionals of excellence. I could directly contact with patients, which was particularly interesting and made me learn a lot. Professionally, I acquired important organizational and methodological tools that I hope will help me in the future. Therefore, I conclude that I was able to reach the objectives that I established and finished my training successfully.

In the future, I want to continue my activities in clinical trials coordination and in project management.

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