Universidade de Aveiro
Ano 2015

Secção Autónoma das Ciências da Saúde

ANA ISABEL SANTOS AUGUSTO

# ESTÁGIO CURRICULAR NUMA UNIDADE DE FARMACOLOGIA CLÍNICA

# CURRICULAR INTERNSHIP IN A CLINICAL PHARMACOLOGY UNIT

**Universidade de Aveiro**
**Ano 2015**

Secção Autónoma das Ciências da Saúde

**ANA ISABEL SANTOS AUGUSTO**

# ESTÁGIO CURRICULAR NUMA UNIDADE DE FARMACOLOGIA CLÍNICA

# CURRICULAR INTERNSHIP IN A CLINICAL PHARMACOLOGY UNIT

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

Dedico este trabalho aos meus pais, Isabel e Filipe,
a quem devo grande parte do que sou hoje.

**o júri**

| | |
|---|---|
| presidente | Doutor Bruno Miguel Alves Fernandes do Gago<br>Professor Auxiliar Convidado, Secção Autónoma de Ciências da Saúde, Universidade de Aveiro |
| vogal - arguente principal | Professora Doutora Alexandra Isabel Cardador Queirós<br>Professora Coordenadora sem Agregação, Escola Superior de Saúde, Universidade de Aveiro |
| vogal - orientador | Professor Doutor José Carlos Fontes das Neves Lopes<br>Professor Auxiliar, Departamento de Física, Universidade de Aveiro |

**agradecimentos**

Os meus agradecimentos vão para todos aqueles que de alguma forma acompanharam o meu percurso académico e contribuíram para o sucesso do mesmo.

Ao Professor Doutor Joaquim Ferreira pela oportunidade, orientação e conhecimentos transmitidos ao longo do estágio.

Ao Professor Doutor Luís Almeida e ao Professor Doutor Bruno Gago pela oportunidade de participar no Mestrado em Biomedicina Farmacêutica.

Ao Professor Doutor José Carlos Lopes pela paciência, dedicação e conselhos na elaboração do presente documento.

Ao Dr. Mário Miguel Rosa, à Dra. Ana Marta Anes e à Dra. Nádia Espada Gomes pela simpatia com que me acolheram na unidade, apoio, disponibilidade e pela oportunidade de formação. À Dra. Ana Noronha pela amizade, pelo apoio e por me ter convidado a participar num projeto desafiante. Ao Dr. Daniel Caldeira pela oportunidade de integrar os seus projetos, disponibilidade e conhecimentos transmitidos. À Dra. Ana Teresa Santos, à Dra. Nilza Gonçalves, e à Dra. Daisy de Abreu pela disponibilidade e oportunidade de aprendizagem. Foi um prazer trabalhar com todos.

À Andreia Vilaça pela amizade incondicional, companheirismo e apoio desde os primeiros dias em Aveiro, sem ti todo este percurso teria sido muito mais difícil. Nunca será suficiente, mas obrigada por tudo.

À Maria Gillies pela irreverência, apoio, compreensão, conselhos, preocupação e amizade que os anos e a distância nunca abalaram. Que assim seja por muito tempo.

À Margarida Vicente que esteve sempre presente e que me ensinou a relativizar a vida. Obrigada por toda a ajuda e apoio ao longo destes anos.

À Anabela Farrica pela cumplicidade e amizade durante toda esta aventura, que espero que perdure.

Ao Vítor Vieira, ao Guilherme Luz e à Joana Oliveira pela amizade e principalmente pelas aventuras e boas memórias que recordarei para sempre com muito carinho.

Ao Márcio Barra pela amizade, pelo apoio e por toda a ajuda ao longo do estágio.

À Adriana Ferreira, à Andreia Rocha e à Carla Rodrigues pela amizade e bons momentos ao longo do estágio.

Ao Professor João Silva pela amizade, motivação e por ter acreditado sempre em mim ao longo de todos estes anos.

À Bárbara Matos, que me fez ver a vida e o Mundo com outros olhos. Obrigada pelo carinho, apoio incondicional, compreensão, motivação, dedicação, paciência e por me conheceres melhor do que ninguém.

À minha família que sempre me apoiou incondicionalmente em todos as decisões, sonhos e ambições.

À minha Mãe, pilar da minha vida, agradeço todo o amor, esforço, paciência, compreensão, dedicação e por ser um exemplo de mulher.

Ao meu Pai, homem da minha vida, pelo amor, por tudo o que me permitiu alcançar e pelo orgulho que tem em mim.

À minha Avó Maria e ao meu Avô Mino, pelo carinho, pelos mimos, pelas histórias e conhecimentos que me transmitiram e por acreditarem sempre em mim.

Às minha manas, Didi e Nônô, que são as meninas dos meus olhos e o meu maior orgulho. Obrigada por tornarem a minha vida mais brilhante e doce. O futuro pertence-vos.

**palavras-chave**

assuntos regulamentares, ensaios clínicos, farmacovigilância, investigação clínica, *medical writing*

**resumo**

O presente relatório de estágio descreve detalhadamente a minha experiência no estágio curricular realizado na Unidade de Farmacologia Clínica do Instituto de Medicina Molecular, desde 13 de Outubro de 2014 até 5 de Junho de 2015. Este estágio foi realizado como parte do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Durante o decorrer desta experiência, tive a oportunidade de participar em diversos projetos em colaboração com diferentes equipas, destacando-se as atividades relacionadas com a submissão de um ensaio clínico em Portugal e as atividades no âmbito da formação em Farmacovigilância.

Este estágio possibilitou-me pôr em prática os conhecimentos obtidos durante a minha formação académica e aprofundar o meu conhecimento sobre investigação clínica, numa perspetiva prática. Para além disso, permitiu-me melhorar as minhas competências e perceber os meus interesses, capacidades, pontos fracos e fortes.

Concluindo, posso afirmar que este estágio foi uma aprendizagem excelente e uma experiência de grande valor a nível profissional e pessoal, tendo conseguido atingir e ultrapassar os principais objetivos estabelecidos.

**keywords**

regulatory affairs, clinical trials, pharmacovigilance, clinical research, medical writing

**abstract**

The present internship report is a detailed description of my experience in the curricular internship performed at the Clinical Pharmacology Unit of the *Instituto de Medicina Molecular*, from October 13th 2014 to June 5th 2015. This internship was performed as part of the second and final year of the Master's Degree in Pharmaceutical Biomedicine of the University of Aveiro.

During the course of the experience I had the opportunity to participate in several projects in collaboration with different teams, most relevantly the activities related to the regulatory submission of a clinical trial in Portugal and related to the training in Pharmacovigilance.

This internship has allowed me to put into practice the knowledge acquired during my academic training and deepen my knowledge on Clinical Research in a practical perspective. Additionally, it has also allowed me to improve many of skills and to understand my interests, capacities, weaknesses and strengths.

In conclusion, I can affirm that this internship was an outstanding training and a very valuable professional and personal experience, for the main established objectives were achieved and exceeded.

## Table of Contents


**1. INTRODUCTION 1**

**2. VISION OF THE HOST INSTITUTION 3**

2.1. *INSTITUTO DE MEDICINA MOLECULAR* ..... 3
2.2. CLINICAL PHARMACOLOGY UNIT (JOAQUIM FERREIRA LAB) ..... 3
2.2.1. CLINICAL TRIALS SUB-UNIT ..... 4
2.2.2. SAFETY AND DRUG UTILISATION RESEARCH SUB-UNIT ..... 4
2.2.3. BIOSTATISTICS AND METHODOLOGICAL SUB-UNIT ..... 5
2.2.4. DRUG EVALUATION AND SYSTEMATIC REVIEWS SUB-UNIT ..... 5

**3. ASPECTS OF MEDICINES DEVELOPMENT AND SAFETY 7**

3.1. CONSIDERATIONS ABOUT CLINICAL TRIALS ..... 7
3.1.1. CLINICAL RESEARCH EVOLUTION ..... 8
3.1.2. CREATING A CLINICAL TRIAL ..... 9
3.1.3. GETTING THE LEGAL AND ETHIC APPROVALS FOR A CLINICAL TRIAL ..... 11
3.1.4. CONDUCTING A CLINICAL TRIAL ..... 13
3.1.5. CLINICAL DATA MANAGEMENT ..... 15
3.1.6. CLINICAL TRIALS IN PORTUGAL ..... 16
3.2. CONSIDERATIONS ABOUT PHARMACOVIGILANCE ..... 17
3.2.1. HISTORIC REVIEW ..... 18
3.2.2. REGULATORY ENTITIES AND ORGANISATIONS ..... 19
3.2.3. PHARMACOVIGILANCE LEGISLATION ..... 21
3.2.4. TOOLS IN PHARMACOVIGILANCE ..... 22
3.2.5. NATIONAL PHARMACOVIGILANCE SYSTEM ..... 23
3.3. OVERVIEW OF MEDICAL WRITING ..... 24

**4. DEVELOPED ACTIVITIES 27**

4.1. SAFETY AND DRUG UTILISATION RESEARCH SUB-UNIT ..... 27
4.2. BIOSTATISTICS AND METHODOLOGICAL SUB-UNIT ..... 30
4.3. CLINICAL TRIALS SUB-UNIT ..... 32
4.4. OTHER ACTIVITIES ..... 35
4.4.1. TRAINING SESSION ABOUT THE *INSTITUTO DE MEDICINA MOLECULAR* ..... 35
4.4.2. WEDNESDAY AFTERNOON MEETINGS ..... 35
4.4.3. CLASSES ABOUT THERAPEUTIC RESEARCH IN NEUROSCIENCES ..... 36
4.4.4. SUPPORT ACTIVITIES ..... 36

**5. DISCUSSION 37**

**6. CONCLUSION 41**

**7. REFERENCES 43**

## List of Figures

Figure 1. Gantt chart with the schedule and duration of the internship activities ..... 27

## Abbreviations

**ADR** Adverse Drug Reaction

**AE** Adverse Event

**AIDFM** Association for Research and Development of the Faculty of Medicine (*Associação para a Investigação e Desenvolvimento da Faculdade de Medicina*)

**CDM** Clinical Data Management

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

**CHMP** Committee for Medicinal Products for Human Use

**CIOMS** Council for International Organizations of Medical Sciences

**CNPD** National Data Protection Authority (*Comissão Nacional de Proteção de Dados*)

**CPU** Clinical Pharmacology Unit

**CRF** Case Report Form

**CRO** Contract Research Organisation

**DGRM** Department of Medicine Risk Management (*Direção de Gestão do Risco de Medicamentos*)

**DSUR** Development Safety Update Report

**EBM** Evidence-Based Medicine

**EEC** European Economic Community

**EMA** European Medicines Agency

**EU** European Union

**FDA** Food and Drug Administration

**FMUL** Faculty of Medicine of the University of Lisbon (*Faculdade de Medicina da Universidade de Lisboa*)

**GCP** Good Clinical Practice

**GVP** Good Pharmacovigilance Practices

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

**ICSR** Individual Case Safety Report

**IMM** *Instituto de Medicina Molecular*

**INFARMED** National Authority of Medicines and Health Products (*Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.*)

**LFCP** Laboratory of Clinical Pharmacology and Therapeutic (*Laboratório de Farmacologia Clínica e Terapêutica*)

**MA** Marketing Authorisation

**MAH** Marketing-Authorisation Holder

**MedDRA** Medical Terminology for Drug Regulatory Authorities

**NCP** National Centre of Pharmacovigilance (*Centro Nacional de Farmacovigilância*)

**NPS** Pharmacovigilance National System

**PBL** Problem-Based Learning

**PI** Principal Investigator

**PRAC** Pharmacovigilance Risk Assessment Committee

**PSUR** Periodic Safety Update Report

**QMS** Quality Management System

**RNCES** National Network Of Ethics Committees (*Rede Nacional de Comissões de Ética para a Saúde*)

**RNEC** National Register of Clinical Trials (*Registo Nacional de Estudos Clínicos*)

**RPU** Regional Pharmacovigilance Unit

**SAE** Serious Adverse Event

**SNS** National Health Service (*Serviço Nacional de Saúde*)

**SOP** Standard Operating Procedure

**SPC** Summary of Product Characteristics

**SUSAR** Suspected Unexpected Serious Adverse Reaction

**SVIG** Database of the Pharmacovigilance National System (*Base de Dados do Sistema Nacional de Farmacovigilância*)

**UFLVT** Lisbon and Tagus Valley Regional Pharmacovigilance Unit (*Unidade de Farmacovigilância de Lisboa e Vale do Tejo*)

**UMC** Uppsala Monitoring Centre

**UN** United Nations

**UNESCO** United Nations Educational, Scientific and Cultural Organization

**USA** United States of America

**WHA** World Health Assembly

**WHO** World Health Organization

**WHO-ART** WHO Adverse Reaction Terminology

**WMA** World Medical Association

## 1. Introduction

The present document is a report about my curricular internship as part of the second year of the Master's Degree in Pharmaceutical Biomedicine of the University of Aveiro. This internship was performed in the Clinical Pharmacology Unit (CPU) of the *Instituto de Medicina Molecular* (IMM), from October 13th 2014 to June 5th 2015.

The aim of this internship was to consolidate and improve the knowledge about Clinical Research, including Clinical Trials, Pharmacovigilance and Medical Writing, and to acquire new skills in a real work environment.

The learning outcomes for this on-the-job experience on the CPU were defined in the beginning of the internship and have been being improved in order to meet the new challenges and activities proposed during its course. Hereupon, the final learning outcomes defined for this internship are described below:

- Improve the knowledge and skills in Pharmacovigilance and acquire qualifications to perform the daily activities of a regional unit integrated in the Pharmacovigilance National System;
- Acquire knowledge about all the procedures and steps to obtain the legal approvals and ethic opinions for a clinical trial;
- Acquire basic knowledge about the functioning of the central statistical monitoring approach in clinical trials;
- Acquire knowledge and skills in Medical Writing and about the process for publication of scientific articles;
- Develop personal, interpersonal and professional skills in an interdisciplinary environment, such as communication, organisation, critical thinking, problem solving, autonomy, and responsibility;
- Write a scientific paper related to Clinical Research.

The accomplishment of a high level of these learning outcomes at the end of the internship will certainly provide me a very comprehensive training in the mentioned areas as well as a personal and professional growth.

This report is organised in chapters and subchapters, starting with institutional, scientific and academic background, followed by the internship activities and finalising with the discussion and the conclusion.

In the second chapter it is provided an overview of the host institution, which complement this introductory information.

In order to frame the activities carried out, the third chapter is a review about the current knowledge of the main areas that were developed during this period. Hereupon, the three main

sections are as follow: Clinical Research - with its conception, evolution, the development of a clinical trial, and clinical data management as its main points; Pharmacovigilance – with a brief mention on its historical perspective, its regulatory environment and regulatory entities in the European Union (EU), the Pharmacovigilance National System (NPS), and the European legislation for Pharmacovigilance; and Medical Writing - which describes the general process, from manuscript writing to scientific article publishing.

Therefore, on the fourth chapter, the activities developed are described in detail, and distributed by each department I worked at.

Also, the main obstacles faced during this period, altogether with the experience, skills acquired, and learning outcomes achieved are profoundly reviewed in the discussion section, taking into account the initial objectives.

Finally, the report ends with a global conclusion of the internship, with a special emphasis on the professional and personal goals achieved.

## 2. Vision of the Host Institution

As previously mentioned, the curricular internship was performed in the CPU of the IMM and in order to provide the reader an overview about the host institution, in the following paragraphs, it will be provided a brief description about its work units and their main objectives.

### 2.1. *Instituto de Medicina Molecular*

The IMM is an Associated Laboratory of the National Ministry of Education and Science which is mainly supported by national and EU funds, as well as by peer reviewed competitive grants, private donations and industrial partnerships (1). It was created in 2002, as the result of the association of five research units from the Faculty of Medicine of the University of Lisbon (FMUL - *Faculdade de Medicina da Universidade de Lisboa*): the Biology and Molecular Pathology Centre, the Lisbon Neurosciences Centre, the Microcirculation and Vascular Pathobiology Centre, the Gastroenterology Centre and the Nutrition and Metabolism Centre (1).

This private and non-profit association is located on the campus of the FMUL, in Lisbon, being its main mission: the development of basic, clinical and translational biomedical research with the aim to contribute to a better understanding of disease mechanisms, developing novel predictive tests, improving diagnostics tools and developing new therapeutic approaches; the support of scientific postgraduate training of young graduates, doctors and other health professionals; and the support of science communication and the provision of external services in the areas of specialised diagnosis, health expertise, quality control and collaboration in national and international committees (1, 2).

### 2.2. Clinical Pharmacology Unit (Joaquim Ferreira Lab)

The CPU, also known as Joaquim Ferreira Lab, is part of the IMM's research laboratories and was formally created on the 1st of July of 2013, based on the research team from the Neuropharmacology Unit of the Neurological Clinical Research Unit and the members of the FMUL's Laboratory of Clinical Pharmacology (3). This internship was conducted under the supervision of Professor Joaquim Ferreira, director of CPU.

The unit is physically located in the Laboratory of Clinical Pharmacology and Therapeutics (LFCP - *Laboratório de Farmacologia Clínica e Terapêutica*) on the third floor of the Santa Maria Hospital, in Lisbon. Currently, the LCPT is responsible for the "Clinical Pharmacology and Therapeutics" curricular unit of the Integrated Master's Degree in Medicine of FMUL; the collaborators of the sub-units of the CPU cooperate in teaching this curricular unit.

The main mission of the CPU is to contribute to the development of effective and safe therapeutic interventions through the creation of optimised methodologies for the design,

conduction, analysis and report of clinical trials. The main areas of interest include the clinical trials methodology, outcomes, systematic reviews, and the safety and use of medicines (3).

The main work units of the CPU are described in next paragraphs, according with the internal documentation of the sub-units and the information provided by the current collaborators.

### 2.2.1. Clinical Trials Sub-Unit

The Clinical Trials Sub-Unit is located on the sixth floor of the Neurology Department of the Santa Maria Hospital. This sub-unit was created in 1999 and only recently became part of the CPU. Its activity includes the conducting of clinical trials and observational studies of medicines, mainly for neurological disorders, with more than a hundred of studies performed since its creation. Neurological conditions such as Parkinson's disease, Alzheimer's disease, cervical dystonia, Huntington's disease, multiple sclerosis, familial amyloid polyneuropathy, epilepsy, and psychosis are currently under research in this unit.

### 2.2.2. Safety and Drug Utilisation Research Sub-Unit

This sub-unit is part of the CPU since 2013, and it is one of the regional units of the NPS, also known as Lisbon and Tagus Valley Regional Pharmacovigilance Unit (UFLVT – *Unidade de Farmacovigilância de Lisboa e Vale do Tejo*), created in 2003 after the decentralisation of the Pharmacovigilance system in 1999.

The National Authority of Medicines and Health Products (INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.*) has contracted this unit in order to perform actions related to Pharmacovigilance in connection with the NPS. The UFLVT actions cover more than 3,6 million inhabitants. Its main activities include: to receive, classify, process, and validate, attribute causality of the spontaneous notifications; to promote Pharmacovigilance actions and organise related training; to propose pharmacoepidemiologic studies, surveys, and scientific publications; to collaborate with the INFARMED in the NPS; and to promote the safe and rational utilisation of medicines.

In what contractual purposes are concerned, the UFLVT is represented by the Association for Research and Development of the Faculty of Medicine (AIDFM - *Associação para a Investigação e Desenvolvimento da Faculdade de Medicina*), created in 1993 with the development and support of training/formation organised by the FMUL being its main purpose, as well as to promote and support research activities and disclose its results, among others.

In regards to the human resources of the UFLVT, it includes one physician and two pharmacists with training experience in Pharmacovigilance, and an administrative assistant. One of the pharmacists accumulates the function of quality manager.

### 2.2.3. Biostatistics and Methodological Sub-Unit

After the creation of the CPU, the Biostatistics and Methodological Sub-Unit was established in order to support the activities developed by the unit itself. This sub-unit has its main focus on statistics, Clinical Data Management (CDM), Medical Writing, project management, and other support activities. This sub-unit provides statistical support to all research projects, mainly related with design and analysis of clinical trials and systematic reviews and methodological support to the design, conduct, analysis and reporting of clinical research studies and to optimize study design and feasibility.

### 2.2.4. Drug Evaluation and Systematic Reviews Sub-Unit

This sub-unit integrates the Movement Disorders Cochrane Collaboration Review Group. The review group is affiliated to the Cochrane Collaboration, which is an independent, non-profit and non-governmental organisation, operating in more than 120 countries (4). Its mission is to assure the accurate assortment of medical research information in a systematic review approach in order to support the decisions of health professionals, patients and authorities related to health interventions by the Evidence-Based Medicine (EBM) principles (4).

The tasks that are performed in this sub-unit allow the development of databases with updated, concise, reviewed and accessible medical research information.

## 3. Aspects of Medicines Development and Safety

The aim of this chapter is to provide the reader a background about the three main areas involved in the on-the-job training: Clinical Trials, Pharmacovigilance and Medical Writing.

The first area presented is the Clinical Trials, starting with a brief introduction about the subject, including its evolution throughout the years. Also, the main procedures to create, authorise and conduct a clinical trial, and to manage clinical data will be mentioned. The last subsection includes the current state of clinical trials in Portugal.

The Pharmacovigilance section includes a historic review since the early ages to the present day, the regulatory entities and organisations in the EU, the current European and Portuguese legislation, the used tools in the Pharmacovigilance activities, and a detailed perspective of the Pharmacovigilance system in Portugal.

The last subject is the Medical Writing, where the general concepts and the process from the manuscript writing to the scientific document publication or release are described.

### 3.1. Considerations about Clinical Trials

The definition of Clinical Research was never a black and white expression. As a matter of fact, a wide range of definitions were written and published throughout the years - some authors have defended Clinical Research as a set of studies with intervention in humans only; others include any research design that includes human studies or any samples taken from them, and others also include animal studies if the results will be directly applied to humans (5). Some of these definitions may be more valid than others, however, the Patient Oriented Research can be considered as a consensual expression in what concerns the explanation of the term Clinical Research, as it regards the aetiology, prevention, diagnosis or treatment of human diseases conducted in human subjects/populations, either with biological material or information of human origin, having a direct interaction between the subject and the investigator, and that can be considered the most embracing yet specific way to describe it (5).

Clinical Research can be divided in two major categories of studies: the clinical trials (or interventional studies) and the observational studies, its main differences are at the level of medical intervention done on the participants. In fact, clinical trials intends to do an in-depth study of a specific intervention, for instance, a certain medicine, a medical device or a medical procedure, in order to determine its efficacy and safety (6). When doing observational studies researchers do not have any influence on the progress of events, as they only collect the relevant clinical data. Observational studies may be prospective (data collected forward in time) as well as retrospective (data collected in past events from existing source documents) (6). This report will have the interventional studies as its main focus.

The process of developing a new medicine is an extremely slow journey that can take between 10 to 13 years (7). In a primary process, tens of thousands of molecules with a potential interest are identified and studied in laboratory, with one of these molecules being selected to pre-clinical tests (*in vivo* and/or *in vitro*) to identify its main chemical, biological and toxicological properties (7). If that molecule is classified as positive in the previous phase, then it is approved to be included in a clinical trial program. Hereupon, if the molecule is proven to be safe and effective during the clinical trials, it is then possible to be applied for a marketing authorisation (MA) from the regulatory authorities (7).

The need to perform well-designed clinical trials comes from medicine's demand to understand the very basis of diseases in order to optimise diagnostic and therapeutics, using the EBM approach, which is essentially a method used as a starting point for medical decisions in research clinical data outcomes, including randomised controlled trials, meta-analyses, systematic reviews, case-control studies, and all types of empirical knowledge which can support clinical practice.

In the following paragraphs it is provided a vision of all the steps involved in a clinical trial.

### 3.1.1. Clinical Research Evolution

There are some milestones in history of Clinical Research that have contributed to the way we conduct clinical trials nowadays.

The first ever recorded results from a clinical trial date from 250 BC, done by Galen of Pergamon, Greek physician, who observed differences between subjects (recovering or deceased) giving them the same substance in order to see the different outcomes (5). In the 1700s Scottish physician James Lind performed and reported the first ever considered placebo-controlled study with the aim of treating and preventing scurvy (5). Finally, in 1931 American physician James Amberson and his team, introduced the "blindness" concept in their trial with tuberculosis patients, with the randomisation being performed by flipping a coin to determine which group will receive the medicine (5, 8). Fisher has then introduced the concept of randomisation in the first edition of his book *The Design of Experiments* (1935) (5, 9).

In the following years many changes were made regarding the conduct of clinical trials: specific committees were created, ethic documents and guidelines were developed such as the Nuremberg Code (1947) – consequence of the human experiments performed in concentration camps during the Second World War, the Declaration of Helsinki (1964), the Belmont Report (1978), and the Good Clinical Practice (GCP) (1996) (5). The year of 1948 is considered to be the

beginning of the Clinical Research modern era, where the concepts mentioned in the previous paragraphs were officially validated and made way to reduce bias in the clinical results (5).

Many clinical disasters that have happened with commercialised medicines have proved the professionals the utmost importance of a properly designed study and the necessity of taking a high control on medicines before a new marketing approval (5). These questions will be further discussed in detail in the Pharmacovigilance section.

The 1970s and 1980s were very positive years in what the growth of Clinical Research is concerned. However, in the 1990s there was a drastic decline in the number of clinical investigators, forcing the authorities and the government to create granting mechanisms to support professionals in their careers, at the same time they had to create proper training and offer better facilities and equipment to investigation (5).

Currently, the costs of research are steadily increasing, with the economic support on a contrary proportion, making the cooperation between industry, academia, government, non-profit organisations, clinical investigators, patients, payers, physicians, and regulators to be a crucial factor in conducting a clinical trial nowadays (10). Given the facts, these stakeholders must offer different resources to support the research, as money, personnel, supplies, medical equipment, computer support systems, and everything needed to complete the project infrastructure (10), however these resources are not useful without a clear plan to conduct the study.

### 3.1.2. Creating a Clinical Trial

After a brief historical review about Clinical Research made in the previous section it is easy to conclude that the tasks and steps to create a clinical trial are currently somehow more complex and time consuming than they were 25 years ago.

The new Portuguese law regarding the Clinical Research (Law nr. 21/2014, of 16 of April) (11) defines a clinical trial as any systematic study conducted in humans or with individual clinical data, in order to investigate or verify the distribution or the effect of health factors, health states or results, health or disease processes, performance and/or safety of interventions or health services, through biologic, behavioural, social or organisational aspects (11). This law covers all Clinical Research with humans related with medicines, medical devices, cosmetics, food supplements and all the observational studies in Portugal.

There are several elements to be taken into account in order to develop the ideal clinical trial infrastructure, with the following key elements being common to all clinical trials: Investigator recruitment; a team with experience in clinical trials; protocol development support; regulatory approval to conduct the study; GCP requirements - which include the informed consent, a review by an Ethic Committee, protection of the participants' integrity, privacy considerations, training

and qualifications of the investigator, reports of adverse events (AEs); contractual agreements between sponsors, institutions and investigators; a plan of the participant recruitment; proper coordination of all centres and teams of the clinical trial; quality-control systems; data collection, management, and analysis; data standardisation documents; publishing of results; and the registration of clinical trials and results on clinicaltrials.gov (12).

A clinical trial process has four phases that can start with a new potential medicine (which has to be performed during all of the phases before obtaining the MA) or with an already commercialised medicine that might need more in-depth study (for instance, in order to prove safety and efficacy to a new therapeutic indication).

Hereupon, the four stages of a clinical trial are as follow:

- Phase I (Human Pharmacology Trials) – also known as the first-in-man studies, is the phase where a few healthy volunteers or ones in a sick condition and without a therapeutic option are included with the aim of assessing the safety, tolerability, and the pharmacokinetic and pharmacodynamics profile of a new medicine (6, 13);
- Phase II (Therapeutic Exploratory Trials) – aims to assess the therapeutic efficacy and safety of the medicine in patients affected by the disease that is currently in study, in order to select the therapeutic regimen present in the next step, with the selection of participants being done following very strict criteria (6, 13, 14);
- Phase III (Therapeutic Confirmatory Trials) – covers comparative studies in big populations in order to demonstrate the safety, efficacy and therapeutic benefit of a medicine compared to a standard medicine and/or placebo (6, 13, 14);
- Phase IV (Therapeutic Use Study) – includes the studies performed after obtaining the MA which are intricately related with the therapeutic indication approved, and are important to optimise the medicine utilisation and thus increase the knowledge about the medicine (for example, additional medicine or food interactions, dose-response assessment, and unknown AEs) (6, 13, 14).

In the following paragraphs the process to create a clinical trial will be briefly described and divided in the main critical steps.

The processes to create a clinical trial from the start begin with properly nominated research question, which can be formulated either after analysing a research paper, during a medical consultation, in a clinical procedure, during a discussion with other professionals or a seminar (5). All collected evidence is used to formulate the research question posteriorly redefined into a research hypothesis, after some literature review about the subject (5, 15).

The next step covers the elaboration of the clinical trial protocol, which must include and clarify the following aspects: the general information, the background information and

significance, the objectives and its purpose, the study design, the inclusion and exclusion criteria, the characteristics of the treatment, the assessment of safety and efficacy, the adverse event reporting plan, statistical methods, data access, quality control and assurance, ethical considerations, data handling and record keeping, financing and insurance, plans for publication and presentation, conflicts of interest, the timeline, and finally the informed consent (16).

The trial design should be made according to the aims and methodologies defined. The main topics that need to be taken into account in order to properly design a clinical trial are as follow: population, inclusion and exclusion criteria, sites where the study will be performed, control(s) for the study, the endpoints, the type of blinding, and the randomisation method.

The patient population must meet the predefined inclusion criteria, to ensure a homogeneous population (as much as possible) and the study can be performed in one centre (unicentric study) or in multiple centres (multicentric study) or even in multiple countries (multricentric multinational study) (7, 13).

To have a better control over a study, the investigated medicine can be compared with other active medicine and/or with placebo, creating a controlled trial (7). The measures, outcomes and endpoints can be properly defined after some literature research about the subject that is in investigation, which can lead to a step back in the process in order to refine the hypothesis (15).

A "blind" study decreases the risk of bias in the results by omitting the information about the medicine that the patient is receiving. Moreover, it is considered single-blinding if the patient does not know the information and double-blinding if both, patient and investigator are unaware of the treatment (13). In an open-label study all those involved are aware about the administered treatment. The randomisation has several advantages in clinical trials, including the elimination of bias of selection and allocation of participants, the facilitation of blinding, and the maximisation of statistical power (17).

After completing the protocol with all the required information it is then possible to submit an application to obtain the EudraCT (the European clinical trials database) number and to apply for the clinical trial approval by the authorities.

### 3.1.3. Getting the Legal and Ethic Approvals for a Clinical Trial

To perform a clinical trial in Portugal it is necessary to obtain an authorisation from the INFARMED, an ethical opinion from the National Ethics Committee for Clinical Research (CEIC – *Comissão de Ética para a Investigação Clínica*) and an approval from the National Data Protection Authority (CNPD – *Comissão Nacional de Proteção de Dados*). All applications can be submitted in parallel or at separated times, in any order. During the process, there is no

communication between the INFARMED and CEIC or local ethics committees unless requested by one of them.

The new Clinical Research national law (Law nr. 21/2014 of 16 of April) (11) created an electronic platform, named as the National Register of Clinical Trials (RNEC – *Registo Nacional de Estudos Clínicos*), for the online submission of all the applications for clinical trials/studies. This new approach aims to promote the interaction between the different stakeholders in Clinical Research, facilitating and encouraging high quality research development for the benefit of patients as well as the dissemination of national Clinical Research to the general public, professionals and researchers (11, 18). The potential of this platform is enormous since it promises to bring together all the information about the current Clinical Research in Portugal in one location. However, the web portal is not operational yet (19), and the applications are still submitted in paper format and in a CD-ROM.

In the following paragraphs it will be presented a brief description about the different entities, which assess the clinical trials applications.

INFARMED is the competent authority, under the auspices of the Ministry of Health, who evaluates, authorises, regulates and controls the human medicines and health products (medical devices, homeopathic products and cosmetics) in Portugal, in order to guarantee its quality, safety and efficacy and ensure appropriate standards of public health and consumer protection (20). The competent authority has 30 days to assess the clinical trial application; this timeline can be extended in 20 days for medicines with biologic products or components of human or animal origin, medicines for gene or somatic cell therapy, and medicines containing genetically modified organisms (11, 21). If the authority decides to consult an expert group or committee, the timeline can be extended in 50 days (11). No deadline was set for the validation of amendments to the research protocol; nevertheless the national competent authority is invited to respond in 35 days (21). The validation of the submission is included in this timeline. If the application is not considered valid, the INFARMED should inform the applicant in the first 10 days of the timeline with the reasons reported (21). The clinical trial authorisation is only valid in Portugal.

CEIC is an independent and multidisciplinary entity with the aim to ensure the protection of the rights, safety and well-being of participants in clinical trials and clinical studies (of medicines and medical devices, respectively), by issuing an ethical opinion about the research protocols and other related documents submitted. That task can also be delegated to a local ethics committee if considered appropriated by the CEIC. The parameters assessed are the following: the relevance and the design of the study, the benefit-risk profile of the intervention, the ability of the team, the human and material resources of the research centres concerned, the participants compensation for damages, insurance, monetary rewards, recruitment methods, procedure to obtain

the informed consent and autonomy of participants, and the circuit and accessibility of the medicine (22). The deliberation is then communicated to the applicant, to the INFARMED and to the local ethic committees of the sites involved in the research. All applications have a number assigned by CEIC (or the Eudra-CT number) that can be searched by the applicant on the CEIC website in order to consult the evaluation process (23). The ethical opinion is normally issued in 30 days. The applicant can submit a substantial amendment to the protocol during the assessment process, and the new ethical opinion is communicated in 20 days (11). If the application is not considered valid, the CEIC should inform the applicant in the first 10 days of the timeline with the reasons reported (21).

CNPD is also a national independent entity, which has the power to supervise and monitor the compliance altogether with the personal data protection laws and regulations, to guarantee the human rights and the fundamental freedoms stated in the Constitution and the law (24). The submission is made by an electronic form in the CNPD website and the decision is usually communicated 30 days after the submission (11).

The recently created National Network Of Ethics Committees (RNCES - *Rede Nacional de Comissões de Ética para a Saúde*), constituted by CEIC and the local ethic committees, aims to enhance the communication between local committees, to promote the development and support to the activities of the local committees, to decrease the deliberation time and the accumulation of applications, to promote the mutual recognition of the ethic opinions between committees, the discussion about ethics in Clinical Research and clinical practice, the proper training to investigators and health professionals, and to facilitate the sharing of resources, information and good practices between committees (11, 25).

The submission process and the required documents for each entity will be discussed further in more detail in the chapter 4, related to the developed activities.

#### 3.1.4. Conducting a Clinical Trial

After getting the legal and ethics approvals, the study can start in the selected centres. The first step involves an initiation visit, where the sponsor delegates to a representative team the task to go to the centres and therefore explain the procedures to the clinical trial team, in order to answer or clarify any question. The clinical trial team usually includes a Principal Investigator (PI), a Sub-Investigator, a study nurse, a study coordinator, among other professionals, depending on the requirements of the study.

The following step includes the patient recruitment, also called the pre-screening visit, which starts with an explanation about the trial performed by a physician of the team who receives a copy of the informed consent to be read carefully. The informed consent aims to inform and

clarify the participant about all the procedures and data collected during the study, as well about its own rights (16). The participants can leave the clinical trial at any stage of the research without having to explain their reasons.

After analysing the information provided about the clinical trial, if the patient decides to participate in the study, it is necessary to schedule an appointment to sign the informed consent in the presence of the PI.

The screening visit aims to evaluate if the participant fits in the inclusion and exclusion criteria of the research protocol. If the participant meets the defined criteria then following stage is the baseline of the trial.

The treatment period starts after the performance of participants' randomisation (if required in the research protocol) and the appropriate distribution of medication. During this period the participant will need to visit the centre for medical appointments and to collect the necessary clinical data, according with the timeline and the requirements defined in the research protocol.

At the end of the study, the participants can enter in a follow-up phase, and the medicine can be given to them in an open-label approach until is it on the market, if stated in the research protocol.

During the clinical trial process it is the sponsor's responsibility to monitor the study in order to ensure the rights and well-being of participants; to verify if data are accurate, complete, and verifiable from source documents; and if the conduction of the trial is in compliance with the research protocol, with GCP, and with the regulatory requirements (16). The monitoring visits to the centres follow the sponsor's Standard Operating Procedures (SOPs), and a report to the sponsor for each site of the clinical trial should be written by the monitor at the end of the visit (16).

Since Clinical Research is a highly regulated area, all these activities described above follow important international policies, directives and recommendations, such as the Declaration of Helsinki, the GCP of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Directive 2001/20/CE, Directive 2005/28/CE, and Directive 95/46/CE. A brief review about each document will be made in the following paragraphs.

The Declaration of Helsinki (26) was developed by the World Medical Association (WMA) and officially adopted in 1964. The current version is the seventh revision of the document, and was revised in the 64$^{th}$ WMA General Assembly, in October of 2013 (26). The document is considered the cornerstone for Clinical Research, since it states the ethical principles to guide the research involving humans, in order to put the well-being of the study participants before science and society (27). These principles are primarily addressed to physicians however, the WMA advises all the professionals involved in Clinical Research to adopt them (26).

The GCP document was created by ICH in 1996, in order to internationally standardise the ethical and scientific quality requirements for designing, conducting, recording, and reporting clinical trials involving human subjects (16). The guideline also details the responsibilities of the ethic committee, the investigator, and the sponsor and refers the information that must be included in the clinical trial protocol, Investigator's brochure and other essential documents to conduct the study (16). If these standards are followed then it is possible to ensure that the rights, safety and well-being of participants are protected and the clinical data obtained are reliable (5, 16). The ICH-GCP guideline is valid in the EU, Japan and United States of America (USA), which facilitates the acceptance of the clinical data by the different regulatory authorities (16). For clinical investigation with medical devices in human subjects the International Organization for Standardization (ISO) created the ISO 14155:2011 (also referred as ISO-GCP) (28). These international standards are transposed into legal requirements by laws and regulations to each national authority.

The Directive 2001/20/CE (29) currently regulates the Clinical Research in EU, defining the requirements for conducting clinical trials. This directive was transposed into the Portuguese law by the Law nr. 46/2004 of 19th of August, recently revoked by the Law nr. 21/2014 of 16th of April (11), already mentioned.

The Directive 2005/28/CE (30) lays the principles and guidelines for GCP of investigational medicines for human use, and the requirements for the authorisation of manufacture and importation. This directive was transposed into the Portuguese law by the Decree-Law nr. 102/2007 of 2nd of April (31).

The last described legislation in this chapter is the Directive 95/46/CE (32) on the protection of personal data, transposed to the Portuguese law by the Law nr. 67/98 of 26th of October (33) and by the Deliberation nr. 333/2007 of CNPD, this last one regarding clinical trials with medicines for human use (34).

### 3.1.5. Clinical Data Management

The clinical data generated by clinical trials are the "diamond in the rough" of Clinical Research. The management of clinical data has the purpose to generate data of high-quality, reliable and statistically significant, in order to get as much information as possible from the study and to reduce the time of medicine development (35).

A CDM team is involved in all the stages of a clinical trial. Some of the activities in CDM are the following: the design of Case Report Form (CRF) to collect the data, the database designing, the data-entry, the data validation, the management of inconsistencies, the medical coding, the data extraction, the data quality control, and the de-identification/anonymisation of data

(35). The data quality control and the de-identification activities will be the focus of this section, with a brief description on the following paragraphs.

The data quality control procedures has the identification of data processing as its main purposes, data entry or coding errors; protocol deviations; missing data; early withdraws; and problems with the database. After the identification of these problems they shall be reported with feedback to the data managers, biostatisticians, and clinical trial team (36).

To prevent the participant's identity to be linked to clinical data is possible to apply specific techniques; de-identification is one of the approaches that can ensure that. Before going any further is necessary to understand that de-identification is different from anonymisation. The de-identification approach refers to a severing of a data set from the identity of the participant's; however, the identifying information can be preserved and could be re-linked by a trusted entity in specific circumstances (37). The anonymisation approach refers to irreversibly severing a data set from the identity of the participant's to prevent any potential re-identification, even by a trusted entity (37).

There are several main steps to implement a de-identification system. The first step is to collect, clean and organise the data; the second step is to select the identifiers from the data set; and the third step is to calculate the identifiability level through the assessment of the replicability, resource availability, distinguish and risk assessment (38). The methods of de-identification can be divided into statistical (statistical and scientific principles and methods) or heuristic methods (rules to distinguish between variables to generalise and variables to exclude from the data set), in a simpler way, the data can be de-identified by removing most of the identifiers or the critical ones; coding and encryption; statistically confirming an unlikely identification; and aggregating data (39-41). After the de-identification process being completed is necessary to assess the risk of re-identification (39).

The processed data obtained after all these steps and methods can result posteriorly in a scientific paper, for example. The importance of data sharing and the Medical Writing area will be discussed further in section 3.3.

### 3.1.6. Clinical Trials in Portugal

The current state of clinical trials in Portugal is still far from the optimal results and from the potential of the country. The percentage of clinical trials per million people in Portugal is among the lowest in Western Europe (42).

Between 2006 and 2014 the number of clinical trials submitted for approval dropped from 160 to 127, with 2011 being the year with less submissions (88 trials) (42).

Most of the performed clinical trials are sponsored by the pharmaceutical industry, and in 2012 the economic investment reached a value of 36 million euros, resulting in a 3,5 million euros saving for the public expenditure in medicines and supplementary diagnosis procedures (42). In that year, more than 1000 jobs in the country were dedicated to clinical trials (42). The academic (non commercial) clinical trials are still a very small percentage (42).

In terms of clinical development phases most of clinical trials applications submitted for approval are phase III studies (42).

The main factors to the declination of clinical trials in Portugal are the weak capacity of patient recruitment and the complexity of legal procedures (loss of competitiveness) (43).

However, not everything is as bad as it seems, the average time for decision by INFARMED has been decreasing over the years, being 33 days in 2014. Nevertheless, it is necessary to improve the global approval duration of clinical trials in Portugal (on average, above 70 days) (42).

Due to the current state of Clinical Research in Portugal, some proposals and conclusions have been presented in reports and analyses about the subject, such as the definition of a strategic outline and a political programme for clinical trials, the reassessment of the current financial incentives and plans for Clinical Research, the regulation review to decrease the approval time, the creation specialised structures to manage Clinical Research, the improvement of conditions to perform studies in primary care, and last but not least, the adjustment of health professionals careers and work schedules to the particular needs of Clinical Research (42, 43).

### 3.2. Considerations about Pharmacovigilance

Pharmacovigilance is an area that has been gathering enormous attention not only by the scientific world but also from society in general. However, the attention that is created by social media is not always the best, for the fact that it evokes apprehension in patients and health professionals, and sometimes resulting in reckless actions with more serious consequences than adverse reactions (44).

The World Health Organization (WHO) defines Pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” (45), which aims to ensure the safety of medicines consumers. Currently, spontaneous reporting, intensive monitoring, and database studies can increase the knowledge on Adverse Drug Reactions (ADRs). Moreover, it plays an important role in Clinical Research, since it establishes the medicine safety profile and it is a crucial element to the evaluation made by the regulatory authorities. For instance, during a clinical trial the PI must report any significant ADRs to the appropriate parties. An adverse reaction is thus considered a Serious

Adverse Event (SAE) if it is related with Clinical Research, and if it results in any of the following outcomes: death, life-threatening experiences, inpatient hospitalisation or prolongation, any persistent or significant disability/incapacity, or a congenital anomaly/birth defect (46). Apart from these said conditions, the physician can consider it as a SAE after appropriate medical judgement, for instance, if any surgical intervention is required to prevent one of the mentioned outcomes (46).

In the following paragraphs it is provided a vision about the framework of Pharmacovigilance in Europe and Portugal.

### 3.2.1. Historic Review

The safety of medicines has a long history in what concerns the human being. It is present in the Code of Hammurabi (a Babylonian law code - 2200 B.C.), Homer's *Odyssey*, the Hippocratic Oath, and Galen's writings, which already had a reference to the "*first, do no harm"* concept and showed its deep concern about the use of medicines or plants, and medical procedures (47, 48).

Unfortunately, it was only after Humanity passed through horrific disasters of ADRs, that the discussion started to really matter and create entities and laws to supervise medicines and protect the human health.

In 1906 was created the "Pure Food and Drugs Act", which had its point on prohibiting the commercialisation of adulterated food and medicines to regulate the labelling of products. This law did not mention any requirements about safety and efficacy, however, it allowed the possibility to withdraw medicines in commercialisation by the Food and Drug Administration (FDA) (47, 48).

The "Food, Drug and Cosmetic Act" was the first law to require tests to demonstrate the low toxicity of medicines before commercialisation. It was created in 1938 after the first big iatrogenic disaster caused by poisoning with diethylene glycol, used as solvent in the preparation of the medicine elixir sulphanilamide for streptococcal infections (48, 49).

In the late 1950s the existing clinical safety information about most medicines was still very poor, and that was the reality about the information for thalidomide, primarily prescribed as sedative and hypnotic and, subsequently, used by pregnant women against nausea and to relieve morning sickness (50, 51). Thalidomide was marketed as a very safe medicine in Europe, Australia and Japan, based on the available clinical data. However, in the early 1960s this treatment resulted in more than 10,000 children with severe congenital malformations, such as phocomelia (malformation of limbs), amelia (absence of limbs) and also deformities in ears, eyes, heart and gastrointestinal system (50). The thalidomide's teratogenic action is the most well known disaster, due to the scale and the repercussions in the future.

The medicine was only withdrawn from the market after the first suspicious malformations being presented in a congress and heavily discussed in scientific journals and newspapers (50). The main obstacles to the withdrawal were the reluctance of the pharmaceutical company to accept the malformations as an adverse effect and the 60 different commercial names, which complicated the product identification in the different markets around the world (50).

As an obvious consequence, the use of thalidomide in pregnancy was banned in 1961, although it currently has the treatment of leprosy and multiple myeloma as its therapeutic indications (51). Also, the properties of this medicine are still under study to evaluate the effectiveness in other diseases (51).

The thalidomide tragedy showed how important the safety knowledge is based on rigorous tests, with detailed protocols, before the marketing approval and the continuous safety monitoring, which is also referred as Pharmacovigilance systems (51).

The Sixteenth World Health Assembly (WHA), in 1963, was the meeting in which the resolution WHA 16.36 was adopted and had the purpose to reaffirm the necessity to take actions as much early as possible to lead to a rapid dissemination of information about ADRs. Consequently, in 1968, a project was created by WHO in order to develop a international system to detect prematurely rare ADRs - the "International Program of Adverse Reaction Monitoring" (52). The WHO centre to coordinate the project was first located in the United States of America (USA), in collaboration with 10 other countries so the feasibility of the idea could be commonly understood (47, 52).

The program was renamed to "International Drug Monitoring Programme" and moved to Uppsala, Sweden in 1978 (53). Currently, this program is managed the by the Uppsala Monitoring Centre (UMC), which is an independent organisation and an international centre for services and scientific research, in order to ensure patients' safety and the effective use of medicines, in collaboration with 147 other countries (95% of the global population) (54). One of the main actions of the project was the development of a standard thesaurus to report spontaneous ADRs in a harmonised way (52).

All of these efforts to enhance the safety of medicines for human use have consequently resulted in the withdrawal of several products over the years. However, despite the progress made with the development of Pharmacovigilance, ADRs are still an enormous problem in public health with, due to the rates of morbidity and mortality, and an enormous economic burden.

### 3.2.2. Regulatory Entities and Organisations

There are several entities and organisations that have a major impact in Pharmacovigilance, and which will be described in the next paragraphs with a concise description about them and its main objectives and actions in the regulatory framework.

Primarily we have the European Medicines Agency (EMA) - a decentralised agency of the EU - which aims at the protection and promotion of public and animal health, and is responsible for the scientific evaluation of medicines for humans and veterinary use (55). The main activities of EMA are as follow: MAs, the safety monitoring of medicines, referral procedures (concerns about the safety or benefit-risk balance), inspections, telematics systems, stimulation of innovation and research, and networking with other regulatory authorities and entities (56). Moreover, the EMA establish guidelines and give an input in legislation development.

The Agency has seven scientific committees for medicine assessment; the following two are the ones that have the main impact in Pharmacovigilance. The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing opinions concerning the medicines for human use (57). The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing and monitoring safety issues for human medicines (58).

As mentioned before in the historic review, WHO has a major role in Pharmacovigilance by establishing the International Drug Monitoring Programme. This authority is responsible for leading global health matters, by coordinating the health systems of the member states of the United Nations (UN) (59).

The already mentioned ICH is an initiative between regulatory authorities and pharmaceutical industry, with the aim to discuss the safety, quality and efficacy of medicines in order to achieve harmonisation in the interpretation and implementation of technical guidelines and regulatory requirements. The ICH guidelines related to Pharmacovigilance will be mentioned in following section.

The Council for International Organizations of Medical Sciences (CIOMS) was created in 1949 by the WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO), which create guidelines by several working groups with a big impact in Pharmacovigilance.

The CIOMS working groups are: CIOMS I, International Reporting of Adverse Drug Reactions; CIOMS II, International Reporting of Periodic Drug-Safety Update Summaries; CIOMS III, Guidelines for Preparing Core Clinical-Safety Information on Drugs; CIOMS IV, Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals; CIOMS V, Current Challenges in Pharmacovigilance: Pragmatic Approaches; CIOMS VI, Management of Safety Information from Clinical Trials; CIOMS VII: Development Safety Update Report (DSUR); CIOMS VIII, CIOMS Working Group on Signal Detection.

The Portuguese competent authority, INFARMED, has already been described in the section about Clinical Trials. In what Pharmacovigilance is concerned, the Department of Medicine Risk Management (DGRM - *Direção de Gestão do Risco de Medicamentos*) of the INFARMED is responsible to ensure the functioning of the NPS, more precisely, is responsible to collect, assess, and disclose the information about suspected ADRs (60). The NPS will be discussed further in detail.

### 3.2.3. Pharmacovigilance Legislation

The 197,000 deaths per year in the EU concerning ADRs were the basis for the development of Pharmacovigilance legislation.

The aim of legislation is to reduce the number of ADRs by collecting better safety data on medicines, efficiently assessing safety related questions, performing effective regulatory actions, empowering patients, and increasing the levels of transparency and increasing communication (61).

The current European and national legislation regulating Pharmacovigilance is:

- The Directive 2011/62/EU of 8 June 2011 (62) amends the Directive 2001/83/EC (63), about the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.
- The Directive 2012/26/EU of 25 October 2012 (64) amends the Directive 2001/83/EC (63) regarding Pharmacovigilance.
- These two directives were transposed to the Portuguese law by the Decree-Law nr. 128/2013 of 5 of September (65), which is the 8$^{th}$ alteration to the Decree-Law nr. 176/2006 (66).
- The Regulation nr. 520/2012 of 19 June 2012 (67) about the performance of Pharmacovigilance activities provided in the Regulation nr. 726/2004 (68) and in the Directive 2001/83/EC (63).
- The Regulation nr. 1027/2012 of 25 October 2012 (69) amending the Regulation nr. 726/2004 (68), regarding Pharmacovigilance.

In addition to legislation, there is a guideline with procedures designed to facilitate the performance of Pharmacovigilance in the EU. The Good Pharmacovigilance Practices (GVPs) apply to EMA, to national authorities of EU and to Marketing-Authorisation Holders (MAHs), covering medicines authorised centrally by EMA and medicines authorised by national procedure. The GVP is divided in various modules covering the major processes in Pharmacovigilance: Module I – Pharmacovigilance systems and their quality systems; Module II – Pharmacovigilance

system master file; Module III – Pharmacovigilance inspections; Module IV – Pharmacovigilance audits; Module V – Risk management systems; Module VI – Management and reporting of adverse reactions to medicinal products; Module VII – Periodic safety update report; Module VIII – Post-authorisation safety studies; Module VIII addendum I – Member States' requirements for transmission of information on non-interventional post-authorisation safety studies; Module IX – Signal management; Module X – Additional monitoring; Module XV – Safety communication; and Module XVI– Risk minimisation measures - Selection of tools and effectiveness indicators (70).

There are currently some modules under development, with its release scheduled for 2015: Module XI – Public participation in Pharmacovigilance; Module XII – Continuous Pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication; Module XIV – International cooperation; Module XVI Addendum I – Educational materials (70).

### 3.2.4. Tools in Pharmacovigilance

Throughout the years several tools to facilitate and standardise Pharmacovigilance activities were developed, with some examples of them to be concisely described in following paragraphs.

The Vigibase™ database collects international medicine safety data, which can be used to access global data, in order to compare ADR profiles of medicines, for signal detection, to update Periodic Safety Update Reports (PSURs), and to perform statistical analyses (71). This database is developed and maintained by the UMC on behalf of the WHO. The main data sources in Pharmacovigilance are the Individual Case Safety Reports (ICSRs) from health professionals and patients; the Vigibase™ contains more than 7 million ICSRs (71).

The WHO Drug Dictionary Enhanced and the WHO Adverse Reaction Terminology (WHO-ART) are dictionaries with codes to identify medicines names, to evaluate medicines information (72), and to code clinical information about ADRs (73), respectively.

The ICH has also created the Medical Terminology for Drug Regulatory Authorities (MedDRA), a dictionary to use during regulatory processes, pre and post-marketing actions, and data entry, among other activities (47, 52). This one is used internationally and available in different languages.

The VigiFlow™, also developed by UCM, is a management system for ICSRs designed for national centres included in the “International Drug Monitoring Programme” (74).

The Eudravigilance, launched by EMA in 2001, is an information system to manage the information and to report electronically Suspected Unexpected Serious Adverse Reactions

(SUSARs) occurring during clinical trials (75). The data is analysed at least every month and is published in the European database of suspected adverse drug reaction reports (75).

In Portugal, the INFARMED created a database in 2004 to record the received adverse reactions, entitled as SVIG (48). This Portuguese database is connected with Vigibase™ and Eudravigilance.

### 3.2.5. National Pharmacovigilance System

In 1957, the death of some children for taking an antibiotic, was the trigger for the creation of a pioneer Portuguese legislation (Law nr. 41448/57) which conditioned the market authorisation of new medicines to a prior assessment (48).

However, in the following years, Portugal did not follow the implementation of Pharmacovigilance systems by the OMS. Only after the entrance of the country in the European Economic Community (EEC), in 1986, the conditions were finally met for the creation of a NPS (48). Consequently, the Medicines Regulation (in Portuguese, *Estatuto do Medicamento*) was published in 1991 (Decree-Law nr. 72/91), where the Pharmacovigilance is mentioned for the first time in an official document, establishing the duty of health professionals to report the ADRs (48, 76).

The NPS was created in 1992 (Legislative Order nr. 107/92), with the purpose to collect the information from MAHs and physicians, regarding ADRs. After the creation of the INFARMED in 1993 (Decree-Law nr. 353/93), the implementation and divulgation of NPS was continued by the National Centre of Pharmacovigilance (NCP – *Centro Nacional de Farmacovigilância*) (48, 76).

In 1999, the Ordinance nr. 605/99, defined the new objectives, functions and organisation for the NPS, in order to enhance the spontaneous reporting of possible ADRs. The main action was the decentralisation of the NPS, by the creation of the Regional Pharmacovigilance Units (RPUs) and the Pharmacovigilance Representatives (health professionals promoting the spontaneous reporting) (48).

Those units have technical and administrative autonomy, exercising their activity in collaboration with the INFARMED (collaboration protocols or service agreement). The main activities of these units are the following: reception, classification, processing, validation, and causality of spontaneous report of possible ADRs; divulgation and promotion the Pharmacovigilance activities, and the submission proposals of pharmacoepidemiologic studies regarding the NPS (48). Currently, there are four RPUs, one for each region of Portugal: the Northern Regional Pharmacovigilance Unit, the Centre Regional Pharmacovigilance Unit, Southern Regional Pharmacovigilance Unit, and the, already mentioned, UFLVT (76). The

Autonomous Region of Azores and the Autonomous Region of Madeira report adverse reactions directly to INFARMED.

In 2012, a new legislation of Pharmacovigilance was created, making several changes in the framework of Pharmacovigilance. The main changes were the following: the possibility of patients to report possible ADRs; a more comprehensive concept of adverse reaction (therapeutic errors, off-label use, abusive or inappropriate use, and ineffectiveness); all the ADRs must be reported, regardless of seriousness and expectedness; the creation of a on-line portal to the electronic submission of ADRs, named as Portal RAM; the MA of medicines depends on the submission of a risk management plan; and the health authorities being able to require post-commercialisation studies or additional monitoring to any authorised medicine (48).

The evolution of the NPS and the continuous efforts to enhance the performance of the system resulted in an increase in the number of spontaneous notifications of possible ADRs. During 2014, the NPS received a total of 4618 notifications, an increase of 25% compared to 2013 and of 33% compared to 2012 (77). Of these notifications of 2014, the majority was made by the pharmaceutical industry (2154 notifications), the remaining were notified by physicians and pharmacists, and only a few were reported by nurses and users of the National Health Service (SNS – *Serviço Nacional de Saúde*) (78, 79). In 2014, the UFLVT received 881 notifications (79).

In the first trimester of the current year (2015) the NPS received 1440 notifications, an increase of 31% compared with the same trimester of 2014 (80, 81). In that period of time, the UFLVT received 147 notifications (80). At the conclusion of this report, this was the only information available by INFARMED regarding the notifications received by the NPS in 2015.

### 3.3. Overview of Medical Writing

Medical Writing includes all the activities that involve writing scientific documents, such as regulatory and research-related documents; educational and promotional literature about medicines and diseases; journal manuscripts and abstracts; content for healthcare websites, or health-related magazines or news articles (82). This activity requires connection and collaboration between stakeholders, resources, and a great deal of effort (83).

The level of scientific information provided in these documents depends of the target audience (patients, general public, physicians or regulators). Therefore, a medical writer has to know and understand the medical terminology and concepts, the relevant guidelines for the structure of specific documents, how to search in medical literature, the clinical data and how to present it, ethical and legal issues, the process of reviewing and editing documents, and the requirements to submit the document for publishing (82). All of these requirements and abilities to be a competent medical writer are not useful without good writing skills.

The writing of a scientific document starts with understanding the purpose of the document and goals to achieve through it, including deadlines, required data, and review process (82). The next step is the literature search and review of information, to support the document writing.

After this initial phase, the writing itself starts with the first draft, usually the most time consuming version, since it is necessary to get familiar with the structure and the specific requirements of the document (82). A senior medical writer, an expert in the subject, usually makes the review process and the quality check of the content (82).

The pre-final stages imply the manuscript formatting and editing (language and grammar), according with the requirements for publishing, if applicable (82). The final step regards the document publishing or release, made by an expert after the approval of the final manuscript.

Medical Writing allows data sharing, which is encouraged in order to provide new knowledge to researchers, sponsors, data repositories, scientific community and general public (83).

## 4. Developed Activities

The activities developed during this internship have covered several different areas, allowing me to also have the opportunity to work with different sub-units of the CPU and to communicate and work in a multidisciplinary environment. The internship started in the Safety and Drug Utilisation Research Sub-Unit (also known as UFLVT) with the duration of one month. Posteriorly, I've moved to an open workspace where I've started working with the Biostatistics and Methodological Sub-Unit in the CDM and Medical Writing area. Later on, I had been proposed to collaborate on a project with the Clinical trials Sub-Unit, which occupied most of the internship duration. In May, I have started the second phase of the internship in Pharmacovigilance, however I have continued to work in the projects related to Medical Writing and Clinical Trials.

The schedule and duration of the activities is identified in the Gantt chart presented below.

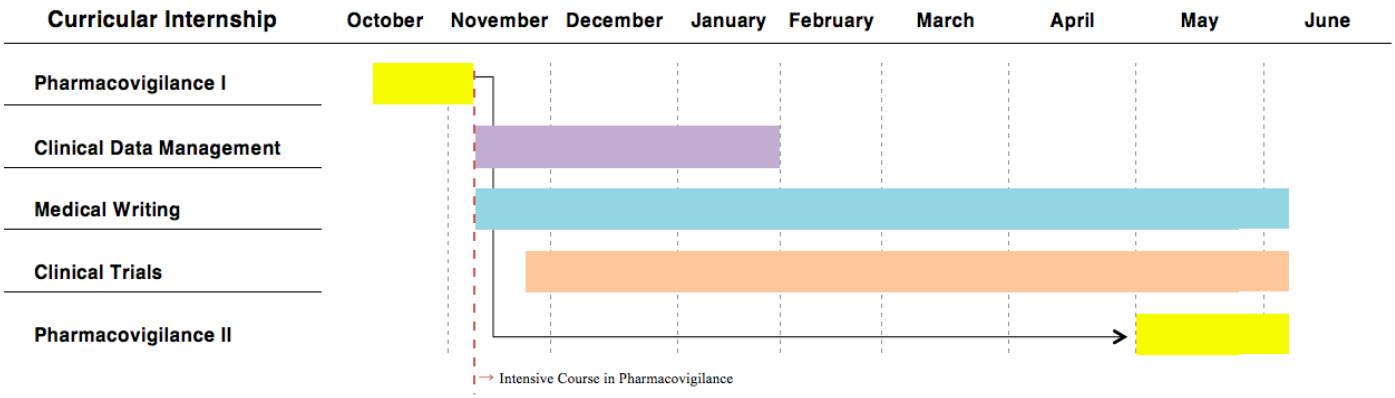


**Figure 1. Gantt chart with the schedule and duration of the internship activities**

The following sections illustrate the activities that were developed, each divided by the units I have worked in.

### 4.1. Safety and Drug Utilisation Research Sub-Unit

The internship started in October in the UFLVT with two planned main phases. The first phase lasted for one month, and it is the one I have started my training in Pharmacovigilance in. First, with an introduction about the area, then through a brief oral explanation by Dr. Ana Marta Anes (coordinator of the ADR Spontaneous Reporting Sector in the UFLVT) as well as by reading some related scientific literature and guidance, as for instance, the book *Farmacovigilância em Portugal* (84), which is related to the NPS and the GVP guidelines. After the introductions were done, I had the opportunity to be familiarised with the Quality Management System (QMS) which was directed by Dr. Nádia Espada (the manager for quality in the UFLVT), who allowed me to

have access to the QMS documentation (quality manual, processes, procedures, work instructions, document models, and records) and explained it to me. This introduction was a good starting point to recall some concepts related to Pharmacovigilance and Quality Assurance and its application to the work reality of a regional Pharmacovigilance unit integrated in the NPS.

After the initial training I was able to start to collaborate in the daily activities of UFLVT. The first task that I was assigned to was the collection of data for the elaboration of the initial report of a few spontaneous notifications, including the collection of the Summary of Product Characteristics (SPC) and the registration of the case information.

One of the notifications that I had the opportunity to analyse was related to a severe ADR, a DRESS syndrome (or Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome). This syndrome is a severe idiosyncratic ADR with a long latency period, characterised by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas (85). Since it is a rare and severe medical condition I was challenged to prepare a presentation in order to inform the UFLVT collaborators and to raise awareness about the DRESS syndrome. To achieve this challenge I had to do an extensive literature research to obtain the most recent information about the medical condition in order to make a clear and intelligible presentation. After the oral presentation, I was congratulated for the way I introduced the subject, for the new information that I provided and for the discussion that was raised between the collaborators.

I also had the opportunity to answer to an information request of a health professional, concerning the relation between an ADR and 3 different medicines. To answer the questions, I had once again to do a literature research about the ADR and the medicines, I had to analyse the SPCs to understand the possible adverse effects, the relation to the requested ADR, and the interactions between medicines. After collecting and analysing the information, I wrote a summary answering the questions and attaching the relevant original information.

During this stage of my internship, the UFLVT was subject to a quality audit by the INFARMED, which aimed to assess the suitability and efficacy of the implemented QMS comparing with the reference standard (NP EN ISO 9001:2008) (86), the QMS documentation and policy, and the defined objectives. During the audit, the INFARMED identified the QMS areas with potential for improvement. Globally, the QMS implemented in the UFLVT meets all the standards required.

The UFLVT also aims to promote the Pharmacovigilance through specific training related to the NPS and spontaneous notification. Therefore, in the last week of this phase of Pharmacovigilance training I had the chance to help in the public dissemination and preparation of an Intensive Course in Pharmacovigilance organised by the UFLVT, with the duration of four days.

The course took place in an auditorium of the FMUL during the 11th, 12th, 13th and 14th of November 2014. Although no longer working in the UFLVT during the course, I was still invited to attend. The course was lectured by the Dr. Mário Miguel Rosa (medical coordinator in the UFLVT and clinical pharmacology expert in the CHMP of EMA), Dr. Ana Marta Anes, among other health professionals. The main subjects focused and discussed during the course were the following: ADR mechanisms and risk factors; risk-benefit assessment; pharmacoepidemiologic studies; methods of medicines safety monitoring; ADR spontaneous notification; imputation and causality assessment systems; neuropsychiatric, cardiovascular, hematologic, dermatologic, paediatric, gastrointestinal, renal, and hepatic ADRs.

In April, I was also given the opportunity to attend an oral presentation by my internship colleague Carla Rodrigues which was related to the MedDRA term selection (explanation about the dictionary in the subsection 2.2.4.), based on the recent update of the dictionary (version 18.0).

I then returned to the UFLVT in the middle of May, for the second phase of the training in Pharmacovigilance. During this last phase of the internship, I was allowed to help in the main activities of the UFLVT.

Some of the responsibilities of the unit, in what its daily activities are concerned, are the collection, management, and assessment of medicines safety data, which also include the detection of abnormalities in the data and to trigger safety warnings based on the evidence of ADRs. At the end of the day, the collaborators of the UFLVT have the task to protect and improve public health.

When the unit receives a spontaneous notification of an ADR, it can arrive by e-mail, telephone, fax or mail. To be considered as valid, the report must include the following information: identification about the notifier (currently, any person can report an ADR); identification about the patient; the active substance; and a signal or symptom of an ADR. If the report is considered valid the case will be assessed.

The report will be dated, signed and a number code will be assigned. In order to confirm the existence of the notifier and to collect additional information to write the initial report, the UFLVT will contact the notifier directly.

Afterwards, the case will be added to in the SVIG and attached with a copy of the original report provided by the notifier. A reply is sent to the notifier with the confirmation of data reception and acceptance of the report. The data entry on SVIG is communicated to the Pharmacovigilance department of INFARMED.

The medical coordinator of the unit must assess the notification through the analysis of the SPC and the PSUR of the medicine, in order to assign the proper causality category, which is posteriorly included in the SVIG. In accordance, with the Uppsala Monitoring Centre the causality

of an ADR can classified as the following: certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable (87).

Subsequently, a summary report about the case and all the information required will be written, attached to the original notification and archived in the UFLVT archive.

Depending on the finale and gravity of the ADR, the notifier must be contacted by UFLVT in order to update the case until the case is considered finalised. The notifier will be then informed about the causality classification attributed to the notification and if any decision related to the medicine will be made based on the spontaneous notification.

By the end of the internship I was able to autonomously perform some of these daily activities of the unit.

### 4.2. Biostatistics and Methodological Sub-Unit

After the first phase of the training in Pharmacovigilance had been completed, I moved to another room in the LFCP, an open workspace, where I started to work with the Biostatistics and Methodological Sub-Unit in CDM and Medical Writing.

The sub-unit works under the central statistical monitoring approach, where data is checked with advanced statistical methods in order to detect research sites with abnormal data patterns. This approach allows professionals to reveal data issues that may remain undiscovered after source data verification and on-site monitoring visits, and those issues may point to other problems that will need corrective actions; it can highlight problems that may not be detected by key risk indicator methods by comparing centres on all possible variables; it is a cheaper alternative once the data check is made by a coordinating centre, avoiding the need to visit all sites involved (88).

My first task in this unit was to make a literature research related to several methodologies applied in CDM. The first subject was about the methods to perform de-identification in clinical data, and after some research I collected the information and wrote a brief report about the different methodologies. A brief description about the types of de-identification was already made in the chapter 3. Posteriorly, I had to search for guidelines that could be applied to the release of databases to the general public, and I understand that there are no specific guidelines in Portugal for this subject and that the existing information is scarce.

I also had the possibility to work in two projects with the statisticians of the unit, Dr. Nilza Gonçalves and Dr. Daisy Abreu. In one of the projects, a clinical trial about movement disorders, I organised data and performed data entry in a database. In the other project, also a clinical trial related to movement disorders, I collaborated in the creation of a report of a data cut statistical

analysis by filling the report with data obtained through the statistical analysis performed with the SPSS® software.

During November I was proposed to work in several investigation projects on Medical Writing by the Dr. Daniel Caldeira, cardiologist intern. The majority of the projects were systematic reviews related to cardiology.

In order to introduce the subject, the following paragraphs will have a brief description of some concepts related with systematic reviews, which I have learned during the internship.

A review article is a critical and constructive analysis of the previously published scientific literature and data about a specific subject. Its function is to organise, evaluate, and synthesise the literature, and also to identify patterns, trends, research gaps, and recommend new research areas (89). The audience for a review article are experts in the subject analysed, students, beginner researchers, and decision-makers.

There are several types of review articles, such as: the narrative review, which selects, compare and resume studies based on the author's expertise, obtaining results at a qualitative level (descriptive articles); and the systematic reviews, which collects findings from multiple individual studies and analyses it statistically in order to obtain an high quality research evidence and an unbiased analysis (89, 90).

A systematic review process requires several steps that will be described bellow.

The first step is the definition of a proper question, through the clarification of the objectives of the subject under analysis, relevant population and interventions, the comparator group, and the types of studies and outcomes that will answer the question (90). This step includes the PICOS approach (participants, interventions, comparators, outcomes, and study design), which helps to facilitate the process by helping the formulation of pertinent and accurate questions (91). This step is crucial to define the studies inclusion criteria.

The second step is the meticulous searching in the literature. To do an unbiased assessment is necessary to search all the literature, including non-English sources and grey literature (not formally published) (90). Sometimes it is also necessary to search the references of full-text papers.

The third step involves the assessment of studies, after the identification of all possibilities of study. Primarily, the studies are assessed for eligibility based on the defined inclusion criteria and those selected will be assessed in full-text according to the following parameters: methodological quality, using a critical appraisal framework; and reported findings, extracted by a data extraction form (90). Two independent reviewers should make this evaluation.

The following step is to combine results of the included studies. This aggregation of the clinical effectiveness, feasibility, appropriateness and meaningfulness related to the subject

assessed, is known as evidence synthesis (90). For instance, a meta-analysis can be an evidence synthesis, which is a statistical technique performed to estimate the net aggregated benefit of the studies included in that analysis. (92). The main advantages of a meta-analysis are the chance to obtain an unbiased, precise, and transparent synthesis of the empirical data (92).

The systematic reviews can be published in scientific journals and databases. Taking the Cochrane Collaboration as an example, it electronically publishes systematic reviews, offering a quick access to updated articles.

Due to the all mentioned characteristics, the systematic reviews are currently one of the cornerstones of EBM.

In the Biostatistics and Methodological Sub-Unit, the ideas for the systematic reviews came from Dr. Daniel Caldeira's expertise on cardiology, who has always made an explanation about the subject under analysis to all the collaborators involved in the project. My main duties in those projects were the following: selection and analysis of the articles obtained in the literature research, based upon the inclusion criteria; data collection; quality assessment of studies, by the QUADAS tool (93) (design for systematic reviews); writing of the manuscript, based in a deep analysis of the included studies. During this time, I've always had the opportunity to clarify any questions or concerns with Dr. Daniel, in order to improve my skills and the results from my work. All the drafts of the manuscript were sent to Dr. Daniel and later discussed to better develop the final article. In the end of the manuscript writing process, a suitable scientific journal is selected in order to submit the article.

As previously mentioned, the Medical Writing projects which I was involved in were focused in cardiology, most of them specifically related to risk stratification tools for high bleeding in patients with venous thromboembolism, patient satisfaction scales with anticoagulant therapy, and risk of major gastrointestinal bleeding with anticoagulant therapy.

In those projects I also collaborated with Márcio Barra who is project manager in the CPU, and who supported me in all the steps.

In late January, my activities related to CDM had ceased. However, I continued to collaborate with the Dr. Daniel Caldeira and Márcio Barra in the on-going projects until the end of the internship, even during the second part of the Pharmacovigilance training.

### 4.3. Clinical trials Sub-Unit

During my time in the Biostatistics and Methodological Sub-Unit, Dr. Ana Noronha, who is clinical trial coordinator of the Clinical trials Sub-Unit, has challenged me to support her team in the submission of an academic clinical trial to the Portuguese authorities (INFARMED, CEIC and

CNPD). I was quite enthusiastic about the idea and the project, since I have always wanted to work in the area of Regulatory Affairs, and that was the perfect opportunity to apply my knowledge on the subject.

However, my duties have increased over the course of this project and covered many other areas besides the Regulatory Affairs, such as Medical Writing and Project Management.

The project was an extension of a French clinical trial related to the Parkinson Disease therapy, running in France since 2011. My first activity in this project was to update my knowledge on the current legislation and on the application submission process to the national authorities, by analysing extensively the Portuguese and European legal and regulatory framework related to clinical trials, and read the protocol to understand the study. After such procedure I was able to make a list of the required information and documents, based on the study characteristics.

The main information and necessary documents to submit an application to the authorities include: cover letters; confirmation of the EudraCT number; application form; clinical research protocol; protocol synopsis; information about the sponsor, investigator-coordinator, and the principal investigators; investigator's brochure; data about the investigational medicinal product; research sites identification, authorisation and facilities; insurance certificate; financial agreement; participants compensation; and, if available, previous authorisations of the competent authorities or ethics committees in other countries.

Some of the required documents to submit a clinical trial to INFARMED and CEIC must be in English or Portuguese, such as the protocol and synopsis, CRF and informed consent. Since these documents were entirely in French, I was also challenged to do the translation of the documents to Portuguese. This task was really challenging to me, due to the large number of pages and the particular medical, pharmaceutical and statistical terms that were in French, and thus I had to make some research in order to do a better translation.

A clinical trial protocol is the document that describes how the clinical trial must be conducted, and it aims to ensure the safety of participants and the integrity of the obtained outcomes and clinical data. The protocol must include the following information: project summary; general information; rationale and background information; study objectives; study design; methodology; safety considerations; follow-up; data management and statistical analysis; Quality Assurance; expected outcomes; dissemination of results and publication policy; duration of the project; anticipation of problems and limitations; project management; ethics considerations; informed consent forms; budget; financing and insurance; collaboration with other researchers, institutions or organisations; and references of the literature (94).

A CRF is a form/questionnaire filled by the physician for each participant in the study. This document collects the data required and can be electronic or printed, and its design varies

according to the protocol. The collected data is always pre-defined in the protocol and includes demographic and clinical data, collected from the medical history of the patient, the information obtaining during the medical visits, and the procedures contemplated in the protocol. In this project, the CRF was in paper format.

The informed consent is a document, with an information note attached, which must be signed by the participant to be part of the clinical trial. This document should include all the relevant information about the study, the medicine, the safety and risks of the intervention, the expected benefits, and the rights and duties of the participant.

In January, I was invited to participate in a teleconference between the IMM team seconded for the project and the team of the sponsor, in order to be aware of the progress and updates related to the study. This meeting's agenda had the following subjects: presentation of the Portuguese and French teams, financial support and agreements, logistical issues, and delegation of tasks. It was a very important meeting that focused on defining the tasks for each member of the two teams.

During the translation I have also worked with the sponsor of the study in order to get all the necessary documentation, and to provide to the French team the required information. Some of those contacts with the sponsor were related with the assessment's medical scales used in the CRF, which had to be translated or replaced into Portuguese or English versions, and also regarding the financial contract between the sponsor and the IMM.

After the translations had been made, Dr. Ana Noronha revised the documents and some corrections and improvements were made.

The following step was meant to identify and contact the research sites in order to perform the study, in order to assess the feasibility, identify the principal investigators and collect the necessary documentation.

I also contacted the pharmaceutical company that would provide the medicine for the clinical trial, to define the re-encapsulation (for blinding purposes), packaging, labelling and distribution of the medicine. To define that I had to calculate the necessary active medication and placebo throughout the study for all the patients, which are expected to be included in the study. Additionally, I had to create an example of the labelling for the medicine under study and for the placebo, and translate and adapt the template of some documents related to the supply chain management, such as: the e-mail to the sponsor representative about the patients' inclusion to send the medicine to the research centres; the form for the medication acknowledgment of receipt for pharmacies of the research centres; the prescription template to release the medication to the patient; the form for the accounting of the returned medication; and the certificate of the medicine destruction.

Simultaneously, I have continued to collect the information for the submission of the application to the authorities, and I also had to complete and create relevant files, such as the cover letters and the application form, filled in the EudraCT website.

By the time of the submission of this report, I was still working with the sponsor to submit the clinical trial to the Portuguese authorities.

This project was a challenge for me, however the knowledge I acquired during my degree allowed me to work autonomously most of the time. It was the most time consuming and hardworking activity, and required more autonomy and responsibility during the internship.

During my collaboration with the Clinical trials Sub-Unit, I also had the opportunity to insert data in electronic CRFs. As mentioned, these platforms are electronic data collection tools provided by the sponsor of the study to the research centre. The inconsistencies, incoherencies or missed data are reported as data queries, which should be solved or justified by the physicians and the study coordinators.

Due to the translation of the mentioned informed consent, I was later asked to verify and correct a translation of another informed consent, made by the sponsor of the study, that was refused by CEIC.

The activities with the Clinical trials Sub-Unit lasted until the end of the internship.

### 4.4. Other activities

#### 4.4.1. Training session about the *Instituto de Medicina Molecular*

During my internship, as part of the host institution requirements for new collaborators, I had to attend a training session related to the IMM, more precisely, about the institution objectives, policies, hierarchy, departments, and on-going projects. The training session also included a field visit to the facilities of the IMM, including laboratories, scientific equipment rooms, among other departments, which proved to have utmost interest to my experience.

#### 4.4.2. Wednesday Afternoon Meetings

Every other Wednesday, at 6 pm, the CPU members from all the sub-units and other persons who collaborate with the unit had a meeting in the LFCT with the purpose to share and discuss relevant topics and the on-going and future projects. In each meeting, a different collaborator made an oral presentation with a brief discussion with the audience in the end.

The aim of these meetings was to update the whole team about the recent projects, new developments and future expectations, and the discussion provided feedback, opinions and

improvements to the projects leaders and participants. The multidisciplinary team of CPU was a major advantage, since it helped to bring new ideas and different opinions to the discussion.

#### 4.4.3. Classes about Therapeutic Research in Neurosciences

Along with my internship colleagues, we were invited to attend some classes of the Master/Doctorate course in Neurosciences of FMUL. These classes included several subjects related to the therapeutic research in Neurosciences, such as: clinical development of medicinal products; clinical trial design; clinical outcomes and biomarkers; systematic reviews, meta-analysis and critical appraisal of data; research with non-pharmacologic therapeutic interventions; pharmacoeconomics; drug discovery and preclinical development; and Pharmacovigilance.

#### 4.4.4. Support activities

I also had the opportunity to help the CPU with some support activities, such as: translation of documents from English to Portuguese; completing a questionnaire for a research grant call; and a critical analysis of an application for a research grant.

## 5. Discussion

It is now more than recognised that Clinical Research has changed modern medicine in a way that the evolution of medicine throughout the last fifty years has given innumerous possibilities of treatments due to the improvements in the ability to effectively treat or prevent diseases, even in its most deadliest forms. This success has and continues to encourage the enthusiasm and belief in the potential of Clinical Research.

The current high quality of medical care was built with the efforts of investigators and health professionals that have invested great part of their lives in Clinical Research. In practical terms, it all translates to clinical trials, which demonstrate to the scientific community if a medicine, a medical device or a medical procedure is safe and effective. Hereupon, it is easy to understand why Clinical Research is such an important area in medicine and why it has changed in so many forms the way medical practice is conducted nowadays.

The internship presented in this document was performed at a clinical pharmacology unit involving different departments with multiple professionals from different academic backgrounds, a work which has allowed me to contact with different areas related to Clinical Research and understand how they work together with a common goal.

This report has helped me to systematise the background information related to the areas that I have worked with during the internship as well as the performed activities by describing all the projects that I was involved in. Also, it has allowed me to understand my flaws, difficulties, achievements and strengths that have emerged during the internship. However, it is very difficult to describe properly and faithfully all the activities and outcomes of this on-the-job training in a report. The training, the work experience, the knowledge and skills acquired, the professional contacts and connections made, and the professional and personal growth have made this internship an extremely rich and challenging experience.

In the following paragraphs, I will discuss some of the major difficulties and obstacles in carrying out some activities faced during the internship, and also the skills acquired and the achieved level of the learning outcomes defined at the beginning of the internship.

The most challenging activity was the submission of an application for a clinical trial authorisation, which proved to be more difficult and time consuming than initially expected. Since the CPU did not have much experience with the submission of clinical trials, also acting as a model of a Contract Research Organisation (CRO), and due to its duties (described in section 4.3.) in this particular project, I had to research and learn the legal requirements applied to this clinical trial in order to understand its implications. That opportunity helped me to stimulate my critical thinking,

my organisation skills, my autonomy, and also my capacity to transmit the information to other people in the most accurate way possible.

To overcome some difficulties and to speed up the process, I have created some personal tools such as: a table checklist to all the contacts made and the documents required from the Portuguese centres; a template of a declaration about the conditions of the research centres facilities to the sites without a specific template; and a table with all the required information and necessary documents to the clinical trial submissions for each authority. These simple tools helped me to organise my time, my tasks and the information collected. Also, these tools were very useful to communicate the process progress to the other members of the team involved in the project and at the same time to improve and assure the quality of my work.

The necessity to contact multiple entities and professionals has improved my writing and verbal communication skills, once that I honed my dialogue during phone calls and my writing on e-mails making my speech more fluid, simple, assertive and more professional. Also, the translation of extensive documents has helped me to improve my translation skills. The opportunity to read and work several kinds of documentation related to clinical trials has allowed me to understand the complexity of the information required and the necessity to detail all the procedures in order to avoid any misinterpretation.

My participation in this clinical trial project helped me immensely to acquire new skills and improve my personal capacities and the contact with the Clinical trials Sub-Unit has shown me the world of clinical trial coordination and the dynamics of a research centre.

With this project I can affirm that I have acquired strong knowledge about the procedures and steps to obtain the legal approvals and ethic opinions for a clinical trial in Portugal. Moreover, I can also affirm that my objectives for this project were exceeded, due to all the tasks that I performed and the improved skills provided by an outstanding on-the-job training and important experience.

By the end of the internship I could affirm that dealing with this particular part of the regulatory affairs of a clinical trial is not an easy task and requires a lot of concentration, organisation, attention to detail, capacity to deal with unforeseen situations and misunderstandings, ability to solve problems quickly and great communications skills. I believe that these skills are the pressure points of a work related to this area.

For all those reasons and for my performance, after the initial struggles, in this task and the feedback that I obtained from my tutors, made this area of managing the initial steps to establish a project of a clinical trial one of my career interests.

During my training in the Biostatistics and Methodological Sub-Unit I have also felt a few difficulties with some tasks related to statistics, once my training in this area is scarce. However,

the autonomous key ability acquired during my degree in Biomedical Sciences, that was taught according to the Problem Based Learning (PBL) method, helped me to search for information about the subject and learn the basics of statistics that were required to perform my tasks.

The training in this sub-unit, working in a central statistical monitoring approach, allowed me to understand its dynamic and main activities. Also, I acquired knowledge about concepts that I was not familiarised with, such as the de-identification of data, which is a very eye-opening approach to use in Clinical Research, in order to prevent a person's identity from being connected with data itself. By the end of the internship I have acquired basic knowledge about the main functions of the sub-unit and the central statistical monitoring approach. The contact made with the Biostatistics and Methodological Sub-Unit made me more curious about this area and willing to learn more about it. Therefore, in the future I hope to develop the knowledge that I have acquired during this period of time.

The Medical Writing related activities have allowed me to play an active role on projects, and to learn more about the writing of scientific articles and its submission for publication in scientific journals. Those activities have also helped me to improve my writing skills and my capacity to synthesise information. The projects developed in this area, which were related to cardiology and anticoagulation had a high challenging although rewarding level, due to its complexity, potentiality and ultimate importance for Clinical Research and daily medical practice. During these projects in Medical Writing I understand that more than communication and writing skills, it is necessary to be very interested and motivated in order to conduct the investigation and its objectives in an effort to publish, for instance, an article with consistent, updated and profound scientific information, which is imperatively required in this area.

The fact of not having had experience in scientific writing and all the knowledge that I've acquired motivates me to explore the area of Medical Writing in the future.

The internship began and also ended in the UFLVT. The training in Pharmacovigilance has allowed me to obtain knowledge and practical skills in the processing of spontaneous notifications of ADRs, clinical pharmacology, safety monitoring of medicines, iatrogenesis, and also in QMSs and its continuous improvement.

During the time in the UFLVT it was taught me not to have shaped preconceptions. Meaning, the raw data is the only source of information, for the fact that if one assumes something based on a person's interpretation of the data, which can lead to errors, misunderstanding, bias, and elimination of evidence, among other deviations to the data source. I have also improved my knowledge about several subjects related to the Pharmacovigilance area such as: National and European legal framework; European legislation; GVP; NPS and regional units activities, and

interactions with other health organisations or entities; the importance of medicines safety; and the importance of reporting spontaneously ADRs, and its limitations and difficulties.

I have finished my internship as person that capable to autonomously perform some of the daily activities, such as the introduction of data in the SVIG, codification of medical terms according to the MedDRA dictionary, and write causality reports and letters. The time that I spent in the UFLVT allowed me to realise the entire process that is necessary to finalise a spontaneous notification.

The possibility to read the QMS documentation (such as operational procedures, data records and the quality manual) allowed me to understand that it ensures that the work is consistent, it has the best quality possible and it is continuously improved.

The work developed in the UFLVT showed me the importance of teamwork and necessity to write all the data and keep all the data sources in order to track cases, documents and information very quickly and avoid data gaps. Also, during the daily tasks, I understand that is crucial to have attention to detail when you are working with a lot of information from different sources that trigger different actions and result in different outcomes.

The experience related to Pharmacovigilance obtained during this internship allowed me to learn much more than I expected at the beginning. And for the described experience and all the mentioned reasons I consider this training a great work experience and I can imagine myself working in this area in the future.

At the beginning of the internship it was proposed to my colleagues and myself to write an individual scientific paper related to Clinical Research. However, the subject and question for the article never arose and this project never developed. This is the unique failure that I can point during the entire internship. Nevertheless, the work developed with the Dr. Daniel Caldeira has somehow helped overcome the failure of not achieving this goal.

## 6. Conclusion

The present report intends to illustrate my experience in this curricular internship by describing the activities performed, the skills acquired and knowledge obtained during that period.

This internship happened in an interdisciplinary environment, which allowed me to develop my personal, interpersonal and professional skills, such as communication, organisation, critical thinking, problem solving, autonomy, and responsibility. The internship at the CPU provided me the opportunity to contact with multiple areas related to clinical research and multiple professional from different academic areas working in the same projects. Moreover, it has helped me to know and understand my interests, capacities, weaknesses and strengths in a variety of areas, showing me that I appreciate to be responsible for multiple tasks in a project, involving communication with multiple teams.

In global view, the internship was a success due to the skills acquired and the achieved level of learning outcomes. The new tasks and responsibilities, the necessity to manage your own work schedule and the pressure to do your best in all your activities can be stressful and scary sometimes. However, there is no better feeling than hear a compliment regarding your work or understand that somehow your work helped the team or the project to succeed.

I can affirm that my internship was an outstanding training and a valuable professional and personal experience and that I am very grateful for this opportunity. The opportunity to collaborate in bigger projects since their beginning was the bigger challenge during the internship and the task that I liked most, due to the level of demand. This internship gave me more responsibilities than I have ever expected and helped me to improve my personal and professionals skills, and for that reason I am very proud of myself.

This experience became my most important academic and work experiences so far. The daily routine, the amount of work and the responsibilities were very different compared to the routine at university. However, I had adjusted myself to this new reality and its requirements very quickly.

All the acquired skills and the opportunity to improve and apply the knowledge obtained during my Master's Degree has motivated me to exceed my expectations and to learn more and obtain the highest experience possible in this contact with the "world of labour".

After this challenging experience, I am eager to do and learn more and go beyond all possibilities given.

## 7. References


1. 2013 Activity Report. Instituto de Medicina Molecular - Facudade de Medicina da Universidade de Lisboa. 2014.
2. About Us: Instituto de Medicina Molecular - Faculdade de Medicina da Universidade de Lisboa; [cited 2015 28.03]. Available from: http://www.imm.fm.ul.pt/web/imm/aboutus.
3. IMM Report 2013. Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa - Communication Unit 2014.
4. About us: The Cochrane Collaboration; [cited 2015 29.03]. Available from: http://www.cochrane.org/about-us.
5. Glasser SP. Essentials of Clinical Research: Springer International Publishing; 2014.
6. Gallin JI, Ognibene FP. Principles and Practice of Clinical Research: Elsevier Science & Technology Books; 2012.
7. Understanding Clinical Trials. F Hoffmann-La Roche Ltd - GPS Public Affairs. 2013.
8. Amberson JB, McMahon BT, Pinner M. A clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuber. 1931.
9. Fisher RA. The Design of Experiments1935.
10. Forum on Drug Discovery DT, Griffin R, Lebovitz Y, English R, Policy BHS, Medicine I. Transforming Clinical Research in the United States:: Challenges and Opportunities: Workshop Summary: National Academies Press; 2010.
11. Lei n.º 21/2014 de 16 de abril - Aprova a lei da investigação clínica. Assembleia da República - Diário da República, 1ª série — Nº 75 — 16 de abril de 2014
12. Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing An Agenda for 2020: Workshop Summary. Appendix G, Discussion Paper: Developing a Clinical Trials Infrastructure. Institute of Medicine (US) Washington (DC): National Academies Press (US). 2012.
13. Tipos de um Ensaio Clínico: Roche Farmacêutica Química, Lda.; [cited 2015 08.03]. Available from: http://www.roche.pt/portugal/index.cfm/investigacao/fases-de-um-ensaio-clinico.
14. Chin R, Lee BY. Principles and Practice of Clinical Trial Medicine: Elsevier Science; 2008.
15. Developing a Clinical Research Protocol: The Survival Guide: Yale School of Medicine; 2012 [cited 2015 05.03]. Available from: http://medicine.yale.edu/education/osr/mdthesis/guidelines/hypothesis/survivalguide.aspx.

16. ICH Harmonised Tripartite Guideline - Guideline For Good Clinical Practice E6(R1). International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. 1996.
17. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet. 2002;359(9305):515-9.
18. Portaria n.º 65/2015 de 5 de março. Assembleia da República - Diário da República, 1ª série — Nº 45 — 5 de março de 2015.
19. Submissão ao Infarmed: INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.; [cited 2015 09.03]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/submissao_INFARMED.
20. Medicines and health products regulatory authority: INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.; [cited 2015 09.03]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/ABOUT_INFARMED.
21. Comunicação da Comissão — Directrizes pormenorizadas para a apresentação às autoridades competentes do pedido de autorização de um ensaio clínico com um medicamento para uso humano, a notificação de alterações substanciais e a declaração de conclusão do ensaio («CT-1») (2010/C 82/01). Comunicações Oriundas das Instituições, Órgãos e Organismos da União Europeia - Comissão Europeia. 2010.
22. Missão: Comissão de Ética para a Investigação Clínica (CEIC); [cited 2015 09.03]. Available from: http://www.infarmed.pt/portal/page/portal/CEIC/QUEM_SOMOS/MISSAO.
23. National Information: Portugal - General: European Network of Research Ethics Committees - EUREC; [cited 2015 09.03]. Available from: http://www.eurecnet.org/information/portugal.html.
24. O que é a CNPD: Comissão Nacional de Protecção de Dados - CNPD; [cited 2015 09.03]. Available from: http://www.cnpd.pt/bin/cnpd/acnpd.htm.
25. Portaria n.º 64/2015 de 5 de março. Assembleia da República - Diário da República, 1ª série — Nº 45 — 5 de março de 2015.
26. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 64th World Medical Association General Assembly, Fortaleza, Brazil. 2013.
27. Griffin JP. The Textbook of Pharmaceutical Medicine: Wiley; 2009.
28. ISO 14155:2011 - Clinical investigation of medical devices for human subjects -- Good clinical practice [cited 2015 17.02]. Available from: http://www.iso.org/iso/catalogue_detail?csnumber=45557.

29. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities.
30. Commission Directive 2005/28/EC of 8 April 2005 Official Journal of the European Union.
31. Decreto-Lei n.º 102/2007, de 2 de Abril. Diário da República, 1ª série — Nº 65 — 2 de Abril de 2007.
32. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995. Official Journal of the European Communities.
33. Lei n.º 67/98 de 26 de Outubro - Lei da Protecção de Dados Pessoais. Diário da República — I Série-A - Nº 247.
34. Deliberação n.º 333/2007 sobre a protecção de dados pessoais nos Ensaios Clínicos com medicamentos de uso humano. Comissão Nacional de Protecção de Dados (CNPD).
35. Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: An overview. Indian journal of pharmacology. 2012;44(2):168-72.
36. Rondel RK, Varley SA, Webb CF. Clinical Data Management: Wiley; 2000.
37. Fullerton SM, Anderson NR, Guzauskas G, Freeman D, Fryer-Edwards K. Meeting the Governance Challenges of Next-Generation Biorepository Research. Science translational medicine. 2010;2(15):15cm3.
38. Malin B. A De-identification Strategy Used for Sharing One Data Provider's Oncology Trials Data through the Project Data Sphere® Repository 2013.
39. Mattern JM. Degrees of De-identification of Clinical Research Data. Journal of Clinical Research Best Practices. 2011;7(11).
40. Ferrandez O, South B, Shen S, Friedlin F, Samore M, Meystre S. Evaluating current automatic de-identification methods with Veteran's health administration clinical documents. BMC Medical Research Methodology. 2012;12(1):109.
41. Friedlin FJ, McDonald CJ. A software tool for removing patient identifying information from clinical documents. Journal of the American Medical Informatics Association : JAMIA. 2008;15(5):601-10.
42. Ensaios Clínicos em Portugal. APIFARMA - Associação Portuguesa da Indústria Farmacêutica; PricewaterhouseCoopers Portugal. 2013.
43. National Health System & the Pharmaceutical Industry: a Partnership for Life. APIFARMA - Associação Portuguesa da Indústria Farmacêutica. 2014.
44. Harmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. European journal of clinical pharmacology. 2008;64(8):743-52.

45. Pharmacovigilance: World Health Organization; [cited 2015 16.03]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/.
46. The Guide to Human Research Activities - Section 25: Serious Adverse Event (SAE) Reporting. Dana-Farber/Harvard Cancer Center. 2009.
47. Jones JK, Kingery E. History of Pharmacovigilance. Mann's Pharmacovigilance: John Wiley & Sons, Ltd; 2014. p. 11-24.
48. Silva JC, Soares MA, Martins SO. Reações Adversas a Medicamentos - Análise da base de dados do Sistema Nacional de Farmacovigilância (SVIG) 2009 - 2011 - Relatório Final Faculdade de Farmácia da Universidade de Lisboa - INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, IP 2012.
49. Ballentine C. Sulfanilamide Disaster: FDA Consumer magazine; 1981 [cited 2015 29.01]. Available from: http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm.
50. Andrews EB, Moore N. Mann's Pharmacovigilance: Wiley; 2014.
51. Kim JH, Scialli AR. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. Toxicological Sciences. 2011;122(1):1-6.
52. Jeetu G, Anusha G. Pharmacovigilance: a worldwide master key for drug safety monitoring. Journal of young pharmacists : JYP. 2010;2(3):315-20.
53. About UMC: Uppsala Monitoring Centre; 2014 [cited 2015 29.01]. Available from: http://www.who-umc.org/DynPage.aspx?id=96979&mn1=7347&mn2=7469.
54. Report from the WHO Collaborating Centre for International Drug Monitoring WHO Collaborating Centre for International Drug Monitoring - Uppsala Monitoring Centre, UMC. 2014.
55. About us: European Medicines Agency; [cited 2015 14.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid=WC0b01ac058001ce7d.
56. What we do: European Medicines Agency; [cited 2015 14.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42.
57. CHMP: Overview: European Medicines Agency; [cited 2015 14.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&mid=WC0b01ac0580028c7a.
58. PRAC: Overview: European Medicines Agency; [cited 2015 14.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000538.jsp&mid=WC0b01ac058058cb19.
59. About WHO: World Health Organization; [cited 2015 14.03]. Available from: http://www.who.int/about/en/.

60. Direcção de Gestão do Risco de Medicamentos (DGRM): INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.; [cited 2015 14.03]. Available from: http://www.infarmed.pt/portal/page/portal/SOBRE_O_INFARMED/ESTRUTURA_E_ORGANIZACAO/DGRM.

61. Pharmacovigilance legislation: European Medicines Agency; [cited 2015 14.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058058f32d.

62. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011. Official Journal of the European Union

63. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001. Official Journal of the European Union

64. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 Official Journal of the European Union

65. Decreto-Lei n.º 128/2013 de 5 de setembro. Diário da República, 1ª série — Nº 171 — 5 de setembro de 2013

66. Decreto-Lei n.º 176/2006 de 30 de Agosto. Diário da República, 1a série — No 167 — 30 de Agosto de 2006.

67. Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012. Official Journal of the European Union

68. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004. Official Journal of the European Union

69. Regulation (EC) No 1027/2012 of the European Parliament and of the Council of 25 October 2012. Official Journal of the European Union

70. Good pharmacovigilance practices: European Medicines Agency; [cited 2015 15.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp - section2.

71. VigiBase™: Uppsala Monitoring Centre [cited 2015 13.03]. Available from: http://www.umc-products.com/DynPage.aspx?id=73590&mn1=1107&mn2=1132.

72. The WHO Drug Dictionary Enhanced: Uppsala Monitoring Centre [cited 2015 13.03]. Available from: http://www.umc-products.com/DynPage.aspx?id=73588&mn1=1107&mn2=1139.

73. WHO-ART - WHO Adverse Reaction Terminology: Uppsala Monitoring Centre [cited 2015 13.03]. Available from: http://www.umc-products.com/DynPage.aspx?id=73589&mn1=1107&mn2=1664.

74. VigiFlow™: Uppsala Monitoring Centre [cited 2015 13.03]. Available from: http://www.who-umc.org/DynPage.aspx?id=97223&mn1=7347&mn2=7252&mn3=7254.

75. EudraVigilance: European Medicines Agency; [cited 2015 15.03]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000239.jsp.

76. Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Junqueira Polonia J, Costa-Pereira A. [The Portuguese Pharmacovigilance System]. Acta medica portuguesa. 2012;25(4):241-9.

77. Evolução de 1992 a 2014 - Notificações de RAM recebidas no SNF INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.; 2015 [cited 2015 27.04]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/EVOLUCAO_1992_2011/Publicacao site_Total Notificacao_1992_2014.pdf.

78. Evolução de 1992 a 2014 - Notificações de RAM recebidas no SNF, por origem: médicos, farmacêuticos, enfermeiros, utentes e indústria: INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.; 2015 [cited 2015 27.04]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/EVOLUCAO_1992_2011/Publicacao site_Total_tipo_notificador_1992_2014.pdf.

79. Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - Ano/2014: Direcção de Gestão do Risco de Medicamentos (DGRM), INFARMED; 2015 [cited 27/06 2015]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/RELATORIOS_ANALISE_PERIODICA_DADOS/Relatorio_casuistica_anual_2014_V2_final_graficos_ordem_alterada.pdf.

80. Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - 1º T/2015: Direcção de Gestão do Risco de Medicamentos (DGRM), INFARMED; 2015 [cited 05/07 2015]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/RELATORIOS_ANALISE_PERIODICA_DADOS/V2_Relatorio_casuistica_1_T_2015.pdf.

81. Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - 1º T/2014: Direcção de Gestão do Risco de Medicamentos (DGRM), INFARMED; 2015 [cited 05/07 2015]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACO

VIGILANCIA/NOTIFICACAO_DE_RAM/RELATORIOS_ANALISE_PERIODICA_DADOS/Relatorio_1_T_2014_publicacao_casuistica_final.pdf.

82. Sharma S. How to Become a Competent Medical Writer? Perspectives in Clinical Research. 2010;1(1):33-7.

83. Piwowar HA, Becich MJ, Bilofsky H, Crowley RS. Towards a data sharing culture: recommendations for leadership from academic health centers. PLoS medicine. 2008;5(9):e183.

84. Maria VAdJ. Farmacovigilância em Portugal2003.

85. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. The Journal of Clinical and Aesthetic Dermatology. 2013;6(6):31-7.

86. ISO 9000 - Quality management [cited 2015 18.04]. Available from: http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm.

87. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre - Causality Categories: Essential Medicines and Health Products Information Portal - World Health Organization; [cited 2015 19.04]. Available from: http://apps.who.int/medicinedocs/en/d/Jh2934e/15.html.

88. Burzykowski T. Central (Statistical) Monitoring of Randomized Clinical Trials: Hasselt University and International Drug Development Institute, Belgium; 2013.

89. Mayer P. Guidelines for writing a Review Article. Zurich-Basel Plant Science Center. 2009.

90. Hemingway P, Brereton N. Evidence-based medicine - What is a systematic review? 2nd ed: Hayward Medical Communications, a division of Hayward Group, Ltd.; 2009.

91. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS medicine. 2009;6(7):e1000100.

92. Crombie IK, Davies HT. Evidence-based medicine - What is meta-analysis? 2nd ed: Hayward Medical Communications, a division of Hayward Group, Ltd.; 2009.

93. Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology. 2003;3(1):25.

94. Research policy - Recommended format for a Research Protocol: World Health Organization; [cited 2015 19.04]. Available from: http://www.who.int/rpc/research_ethics/format_rp/en/.