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Departamento Ciências Médicas

João Pedro da Silva Almeida

ESTÁGIO CURRICULAR EM INVESTIGAÇÃO CLÍNICA

CURRICULAR INTERNSHIP IN CLINICAL RESEARCH

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de mestre em Biomedicina Farmacêutica, realizada sob a orientação do Professor Doutor Joaquim José Coutinho Ferreira, Professor Auxiliar da Faculdade de Medicina da Universidade de Lisboa, e da Professora Doutora Alexandra Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro.

o júri

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palavras-chave Coordenação de ensaíos clínicos, medical writing, meta-análises, ensaios clínicos, estudos observacionais

resumo

Este relatório apresenta a minha experiência de estágio na Unidade de Farmacologia Clínica onde pude participar em projetos de investigação, essencialmente como "medical writer"**,** "data manager"**,** gestor de projeto e monitor de estudos observacionais e na Unidade Neurológica de Investigação Clínica, onde pude desenvolver atividades de coordenação de ensaios clínicos. O estágio realizou-se entre 15 de setembro de 2015 a 30 de Junho de 2016.

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

Serve o presente relatório para relatar as atividades que tive a oportunidade de desenvolver, nomeadamente de coordenação de ensaios clínicos e estudos observacionais, bem como as atividades de "medical writer"**,** farmacovigilância, entre outras.

No decurso do estágio, tive a possibilidade de pôr em prática os conhecimentos adquiridos ao longo do Mestrado, e aprofundar o meu conhecimento sobre as atividades de coordenação de ensaios clínicos e observacionais.

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

Em conclusão, o estágio permitiu-me pôr em prática o conhecimento adquirido no Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro e serviu como nova fonte de aprendizagem e crescimento profissional e pessoal.

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

Abstract

This report presents my internship experience at the Clinical Pharmacology Unit where I could participate in research projects, mainly as a medical writer, data manager, project manager and monitor of observational studies and at the Neurological Clinical Research Unit, where I could work in coordination of clinical trials.

The internship is part of the curricular activities of the second year of the Masters in Pharmaceutical Biomedicine, University of Aveiro. The internship took place from 15th September 2015 to June 30th, 2016.

This report will address the activities that I performed, namely the coordinating activities of clinical trials and observational studies, or activities related to medical writing.

Throughout the internship, I had the opportunity to put into practice the knowledge acquired during the master's degree, and deepen my knowledge of the coordination activities of clinical and observational trials.

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

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

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
APIFARMA	Associação Portuguesa da Indústria Farmacêutica
CDR	Clinical Dementia Rating
CEIC	Comissão de Ética para a Investigação Clínica (Portuguese Ethics Committee for Clinical Research)
CES	Comissão de Ética para a Saúde
CHDI	Cure Huntington's Disease Initiative
CNPD	Comissão Nacional de Proteção de Dados
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CVD	Cardiovascular Disease
CVMP	Committee for Medicinal Products for Veterinary Use
eCRF	Electronic Case Report Form
EBM	Evidence Based Medicine
EEA	European Economic Area
EMA	European Medicines Agency
ERS Task Force	European Respiratory society Task Force.
EU	European Union
EUCTR	European Union Clinical Trials Register
FMUL	Faculdade de Medicina da Universidade de Lisboa
GCP	Good Clinical Practice
GNP	Gross National Product
HSM – CHLN	Hospital de Santa Maria - Centro Hospitalar Lisboa Norte
IC	Informed Consent
ICH - GCP	International Conference on Harmonization Good Clinical Practice
IMM	Instituto de Medicina Molecular (Institute of Molecular Medicine)

INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web-Response System
LCPT	Laboratório de Farmacológica Clínica e Terapêutica (Laboratory of Clinical Pharmacology and Therapeutics)
MACE	Major Adverse Cardiac Events
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MOOSE	Meta-Analysis Of Observational Studies in Epidemiology
MRC	Medical Research Council
NCRU	Centro de Ensaios Clínicos de Neurologia (Neurological Clinical Research Unit)
NSTEMI	Non ST Segment Elevation Myocardial Infarction
OHFNC	Oxygentherapy High Flow administered by Nasal Cannula
PI	Principal Investigator
PSUR	Periodic safety update reports
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
QATSO	Quality Assessment Tool for Systematic Reviews of Observational Studies
QMS	Quality Management System
RCT	Randomized Controlled Trials
RevMan	Review Manager
RNEC	Registo Nacional de Ensaios Clínicos
RPU	Regional Pharmacovigilance Units
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
STEMI	ST Segment Elevation Myocardial Infarction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
WHO	World Health Organization
WMA	World Medical Association

1. Introduction

In the second year of my Master's degree in Pharmaceutical Medicine, I had two options. To do a project and a dissertation about a defined topic or enrol in an internship. I chose the second option because I had the desire to experience the professional context in order to apply what I learnt in the previous four years of formation. I also want to keep building myself as a person and as a professional with the experience outside academia.

I undertook my 10-month internship at Clinical Pharmacology Unit (CPU) of the Institute of Molecular Medicine (IMM). The CPU is comprised by three main units, and two sub-units. The three main units are the Neurological Clinical Research Unit (NCRU), the Lisbon and *Tejo* Valley Regional Pharmacovigilance Unit which is the Regional Pharmacovigilance Unit, and the Portuguese Branch of the Ibero-American Cochrane Network. The sub-units are the Biostatistics Sub-Unit and the Methodological Sub-unit. This structure allowed me to go through different sections of the laboratory and work in different areas of my formation.

This internship was conducted under the supervision of Professor Joaquim Ferreira and Professor Alexandra Queirós.

This document is the report of 10 months of experiences, activities and projects developed during the internship.

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

1.1. Objectives

As defined in the signed agreement the objectives for this internship were:

- Acquisition of knowledge, skills and qualifications in coordinating clinical trials;
- Acquisition of basic knowledge and skills in clinical data management and clinical data analysis and treatment through processes like systematic review, meta-analysis and medical writing.
- Acquisition of knowledge and skills in the area of pharmacovigilance integration in the processes of the regional unit of the National Pharmacovigilance System;

1.2. Structure of the Host Institution

The internship was held in the Clinical Pharmacology Unit of the IMM.

IMM is a Laboratory Associated to the Portuguese Ministry of Science and Higher Education. Founded in December 2002, It is a Private, Nonprofit Association that resulted from the association of 5 former research units from the Faculdade de Medicina da Universidade de Lisboa (FMUL): 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). Hosting approximately 400 researchers and located in the campus of the FMUL and Santa Maria University Hospital - North Lisbon Hospital Centre (HSM-CHLN), the IMM fosters rigorous and innovative basic, clinical and translational biomedical research. Over the past four years It as published on average 180 articles each year, since its creation in 2002 has 1316 published articles and 21699 citations (1). Emphasis has been given on the quality, instead of quantity, of publications issued by IMM. In 2014, researchers published 193 papers 28 of those in journals of impact higher than 10 and this number has been increasing every year.

Several international as well as national awards have also recognized IMM teams. Amongst the most recent we include the Michael J. Fox Innovation award, the Pessoa Award, the Prémio Nacional de Inovação BES, the Crioestaminal award, the Pfizer Award in Clinical Research, the Bial Award in Clinical Medicine, the Innovator Award of the Kenneth Rainin Foundation, the Grunenthal Award in Pain Research, the Calouste Gulbenkian Foundation award and the Competition Idea to Product award (1).

The CPU is one of the laboratories of IMM and It is composed by:

1. NCRU, sited on the 6th floor of the Neurology department of the Hospital Santa Maria, which conducts clinical trials and other clinical research studies in Parkinson's Disease, Huntington's Disease, Multiple System Atrophy, Stroke, Alzheimer's Disease, Multiple Sclerosis, Epilepsy and Amyotrophic Lateral Sclerosis (ALS);
2. The Portuguese Branch of the Ibero-American Cochrane Network with its expertise in conducting systematic reviews and related clinical trial (CT) methodology issues;
3. The Regional Pharmacovigilance Unit plays a key role in managing drug utilization and safety, being an extension of *Autoridade Nacional do Medicamento e Produtos de Saúde* (INFARMED) on the field, is responsible for receiving and processing secondary reactions of medications;
4. Biostatistics Sub-Unit provides statistical support to all research projects, mainly related with design and analysis of clinical trials and systematic reviews. This subunit supports the work of some projects of the NCRU and investigator driven research.

5. Methodological Sub-Unit who support both NCRU and investigator driven research with the design, conduct, analysis and reporting of clinical research studies and to optimize study design and feasibility.

NCRU was the department were I spent most of my internship. The unit is responsible for conduct clinical trials and observational studies of new drugs for neurological disorders. It was stablished only in 1999 and It was initially independent from the other units of the CPU. Before the establishment of this unit, the Neurology department of the Hospital Santa Maria (where NCRU is now based) already received clinical trials by the hand of Professor Antonio Damásio, and Professor Castro Caldas. Some of this trials back in the sixties include the Levodopa trials, the current gold standard for the treatment of Parkinson's disease, and selegiline, the first selective inhibitor of B-Type Monoamine Oxidase and the first synthetic catecholaminergic activity enhancer drug (2).

An informal union of the NCRU and the CPU (back then called Instituto de Farmacologia e Terapêutica Geral) was set when Professor Cristina Sampaio was invited to work in both units. In the early nineties Dr. Mário Miguel Rosa and Professor Joaquim Ferreira were invited to work in both units. Later Professor Joaquim Ferreira became the leader of Instituto de Farmacologia e Terapêutica Geral, when Professor Cristina Sampaio left the unit to become Chief Medical Officer of the Cure Huntington's Disease Initiative (CHDI) Foundation. In 2002 was created the IMM, and these two units eventually ended up being integrated into the IMM. Through efforts of Professor Joaquim Ferreira, NCRU and Instituto de Farmacologia e Terapêutica Geral joined forces to form the CPU.

Since 1999, NCRU has been involved in a total of 138 neurological clinical and observational, multi-center and multinational studies, in conditions like: Parkinson's disease, Alzheimer's disease, cervical dystonia, Huntington's disease, multiple sclerosis, familial amyloid polyneuropathy, epilepsy and psychosis;

Once that NCRU is located on the Neurology department of the hospital it facilitates the identification of potential candidates through the outpatient clinic of it. The research unit can count with the support of experienced neurologists, psychologists, psychiatrists, and other healthcare professionals, who are essential for conducting clinical trials. There is also an essential link between the NCRU and the hospital pharmacy because the former is responsible for receiving, storing and providing the experimental drugs used in the clinical trials. They also have an important role in assuring the blindness in some of the studies.

1.3. Report structure

The report is structured as follows:

- Chapter 1 – Introduction: in this section I identify the objectives of my internship and characterize the host institution. The report structure is also presented to ease reader comprehension.
- Chapter 2 – State-of-the-Art: in this chapter, I provide some context for the activities developed during my internship. I present general concepts and procedures of clinical research, the concept of what is a clinical trial and the current panorama of clinical trials in Portugal. I also clarify what medical writing and systematic review is.
- Chapter 3 – Developed activities: this is the central chapter of this report where I present all the activities realized during the 10 months of internship. From my experience working as a clinical trial coordinator to the projects I worked on as a medical writer and project manager.
- Chapter 4 – Discussion: this chapter presents a discussion of the internship, and a review of the skills I acquired during these 10 months, and where could I improve upon. I also present my contributions to the hosting entities.
- Chapter 5 – Conclusion.

2. State-of-the-Art

My activities during the internship can be divided into three large groups: Clinical trial coordination, medical writing and pharmacovigilance. These themes are complex to simply start detailing what I did without any background, so it is important to explain the concepts related to a clinical trial, medical writing and pharmacovigilance. As clinical trial coordination was the activity in which I spent most of my time this will be the theme where I will provide more detail. I will also provide some information about the current state of the activity in Portugal.

2.1. Considerations about Clinical Trials

Nowadays clinical research in humans can be divided into two large groups: Observational studies and Clinical trials (or interventional studies).

Observational studies involve the direct observation of individuals in their natural setting, without a direct or indirect intervention from the research team that would alter the normal daily life of the participants. As such, if the participants receive an intervention it is due to is life settings, individual preferences, practice patterns, or policy decisions. They aren't imposed by a research decision nor random allocation of individuals or any defined protocol (3). I participated in the coordination of an observational study that I will describe later however this report will have the interventional studies as its main focus.

By the International Conference on Harmonisation Good Clinical Practices (ICH-GCP) E6 guidance, a clinical trial is "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous." ((4 , p.3). Clinical trials are very useful since, for example, it allows to study a new pharmaceutical product concerning the helpfulness and harmfulness of it, comparing it to available standard treatments or no intervention. Clinical trials help determine the efficacy and safety of new interventions through the measurement of endpoints, like for example, overall survival in a cancer treatment, quality of life assessments in Familial amyloid polyneuropathy (5).

2.1.1. Evolution in clinical trials

Although the clinical trial definition, designs and legislations is now well-defined, that has not always been the case in the past.

Dr. James Lind is considered the first physician of the modern era to have conducted a controlled clinical trial. As a surgeon working on a ship he faced a high mortality of scurvy amongst the sailors. In reaction to that, in 1747 and with basis on his own description he had created a trial that covered the essential elements of a controlled trial (6). Lind selected twelve patients with scurvy. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the fore-hold. After he divided them into groups of 2, the men were given the same rations, but each pair was allocated to a different scurvy treatment: either cider, a weak acid, vinegar, sea-water, nutmeg and barley water, or oranges and lemons. The results were clear: oranges and lemons gave the most sudden and visible good effects (6, 7). In 1811 another milestone would emerge: the placebo. Hooper's Medical Dictionary of 1811 defined it as “an epithet given to any medicine more to please than benefit the patient.” (6 , p.5). But only in 1863, Dr. Austin Flint planned the first clinical study comparing a dummy remedy to an active treatment. He treated 13 patients suffering from rheumatism with an herbal extract which was advised instead of an established remedy (6). In 1943 another breakthrough, the Medical Research Council (MRC) United Kingdom (UK) carried out a trial investigate patulin treatment for (the common cold an extract of Penicillium patulinum). It was the first double blind comparative trial with concurrent controls in the general population. The blindness of the participants and physician was rigorously controlled. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. It was also one of the last trial with non-randomized allocation of participants given that Dr. Austin Bradford Hill, in 1948 introduced the concept of randomized clinical trial, which evaluated streptomycin for the treatment of pulmonary tuberculosis (6, 8). In this study the decision of whether a patient would be treated by streptomycin and bed-rest or by bed-rest alone was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each center by Professor Bradford Hill (6). The modern template of the clinical trial was here established, alongside the concept of a control.

Currently, clinical trials can be classified and divided by study objective and phase (9):

- Human pharmacology trials or Phase I – This phase marks the first time in humans. The objective is to determine the safety (tolerance, pharmacokinetic and pharmacodynamics profile) of the experimental drug. 10 to 30 healthy volunteers;
- Therapeutic exploratory trials or Phase II – Aims to determine if treatment has a therapeutic effect and if the benefits outweigh the risks. Normally a dosage or dosage scheme is

estimated. Preliminary efficacy and safety information is obtained, and the foundations for the pivotal phase III trials are placed. 20 to 50 patients with the target disease;

- Therapeutic confirmatory trials Phase III – Where the objective is to compare new treatment to the standard therapy or a control or placebo (if no standard therapy exists) and to evaluate if it has added value. This phase provides the basis for the assessment of the benefit/risk relationship, and to gather enough information to submit to regulatory authorities for drug approval. 100 to 1000 patients;
- Therapeutic use study or Phase IV – To obtain long-term, large-scale information on morbidity and late effects (post marketing study). Hundreds or thousands of patients;

The study designs used in each phase varies. Nowadays the gold standard of clinical trials is randomized controlled trials (RCT) so much that, it is placed at the top of the list of levels of evidence in evidence-based medicine (9). A RCT is frequently used to test the efficacy or effectiveness of several medical intervention and may provide information about adverse effects. In a RCT individuals are randomly allocated to two or more treatment groups, which usually include a standard treatment group and one or more experimental groups (9). The use of randomization and control are two characteristics of the RCT that ensure good clinical evidence, whether held under the GCP. A scientific validation of comparison between 2 treatment groups requires that the groups are as similar as possible. Without such an assurance, healthier participants may be given one treatment and sicker participants another treatment and the observed results would most definitely be biased in favour of healthier participants. The best way to achieve the required balance is through the use of randomization. Randomization will ensure that a specific treatment assignment is not known in advance to either the clinician or the patient. The principal benefit of randomization is that it will eliminate both conscious and unconscious bias associated with the selection of a treatment for a given patient (5, 9). In the other hand, for a RCT to be controlled the intervention (which can be a pharmaceutical product, a medical device, or a lifestyle intervention) must be compared. Clinical trials usually compare a new medical treatment to a comparable one that is already available on the market, or to a placebo that contains no active pharmaceutical substance. When the outcome can probably be affected by participants or investigator's expectations, then the use of blinding is necessary. There are single blind studies (where the patient is blind), double blind (when the patient and the investigator are blind) and triple blind (when the patient, investigator and data clean-up people are blind). The statistician can only be partially blinded since he has to know which patients are in the same treatment group (5). As mentioned

above, the combination of randomization and blinding are characteristics necessaries for a quality study design. But at times it can be unethical, for example if a study is made in a treatment of a serious disease with no standard of care, to go through a randomization between the study drug and placebo would be unethical. Hence, to go through Institutional Review Board (IRB) is necessary.

In the historical beginning of clinical trials, there were not any type of legal control or legislation. Due to that, the way to the present legislation is full of misfortunes and disrespect of the human being. Between 1939 and 1945, during the World War II experiments were done in the prisoners of the concentration camps without their consent. As a result, the Nuremberg code was developed. The Nuremberg Code is a set of research ethics principles for human experimentation which includes principles as informed consent (IC) and absence of coercion; properly formulated scientific experimentation; and beneficence towards experiment participants (10, 11). The Nuremberg code was not honoured by some researchers and the abuses and exploitations of humans in research continued. An examples of unethical research was the Willowbrook State Study was carried in Willowbrook State School, a New York State institution for people with mental disability. The objective of this study was understand the natural history of infectious hepatitis and subsequently to test the effects of gamma globulin in preventing or recovering the disease. The children, were deliberately infected with the hepatitis virus. At first subjects were fed extracts of stools from infected individuals, later subjects started to received injections of more purified virus preparation to know natural course of infective hepatitis in children (12). This and other crimes led to the creation of the Declaration of Helsinki, a set of guidelines produced by World Medical Association (WMA) to protect the rights and well-being of participants in clinical (11). It states that: “It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research”(13), p.2191). The Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice guidelines establish the ethical guiding principles for conducting clinical research and the necessary guidance to ensure that clinical research is standardized in the world. Both have the participant and his well-being as central importance because they ensure that all clinical research is conduct in willing participants, who were previously informed of the potential risks and benefits of a given intervention, and gave their informed consent (14). The ICH-GCP E6 (4) describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRB. This document emerged in an effort to standardize clinical research in all three ICH regions: The United States of America, Europe, and Japan.

The current legislative for clinical trials is the Directive 2001/20/CE (15) it has all the requirements for the conduct of clinical trials in the EU. This directive was transposed into Portugal law under the Decree-Law 46/2004 of August 19th that was later updated to the Law No 21/2014 of April 16th (16) which was recently amended by the Law No 73/2015 of July 27th (17).

2.1.2. Setting up and running a clinical trial

The process of developing a new medicine is an extremely slow journey that can take between 10 to 13 years (18). A step before going into clinical trials, tens of thousands of molecules with a potential interest are identified and studied in laboratory, with one of these molecules being selected to preclinical tests (in vivo and/or in vitro) to identify its main chemical, biological and toxicological properties (18). If that molecule is classified as positive in the preclinical tests, then it is approved to be included in a clinical trial program.

Due to the heavy regulation and guidelines on clinical trials, setting up and running a clinical trial is very complex. It requires the involvement of a diverse set of stakeholders. The key stakeholders and their role in clinical trials are (19):

- Sponsors: Pharmaceutical companies or academic institutions design, construct, manage and finance clinical trials. However, the completion of clinical trials can be subcontracted.
- Research centers: Public health organizations or private laboratories or other entities that meet the technical means and human resources to carry out the clinical trials. Since most research centers are hospitals, hospital administrations are also a relevant stakeholder to take responsibility for the negotiation of the agreement and approval of conducting a clinical trial on the appropriate center.
- Contract Research Organizations (CROs): The role of CROs scope is diverse and can ensure all development activities or only part, including regulatory activities, monitoring centers / researchers, data management or pharmacovigilance activities throughout the process.
- Research Team: Doctor or other recognized to pursue the research activity. He is responsible for conducting the clinical trial at a trial and to coordinate the technical team involved. The research team is composed by:
    - ¬ Investigators and sub-investigators, must be physicians with proper training and experience in conducting clinical trials. They are responsible for recruiting participants, providing medical care to clinical trial subjects, safeguarding the safety and well-being of the patient during the clinical, prescribing and

administering the investigational product, and resolving queries from the clinical trial.

- Clinical trial coordinator is an integral part of the research team. This professional is responsible for conducting the study in accordance with the protocol and the ethical standards that govern clinical research. As a coordinator of the study, he oversees the development of the entire process in the investigation center. He is responsible for a number of different tasks as: administrative and financial work, preparation of patient visits and responsible for different documents (for example, budget proposals, audit reports, training documents and case reports). This professional facilitates the entire research process, by monitoring the procedures, collecting data and making sure that all the research is done according to the study protocol.
- Study nurse, who is responsible for collecting biological samples from the participants, as well as giving overall support to the study team.
- Hospital pharmacy and the hospital pharmacists, who are responsible for receiving, storing, dispensing and for the accounting of the investigational product.

- Regulatory authorities**:** In addition to the State that defines the sector policy and regulatory framework, including the bodies responsible for sector regulation, namely the INFARMED, the Ethics Committee for Clinical Research (CEIC - *Comissão de Ética para a Investigação Clínica*) and National Data Protection Commission (CNPD - *Comissão Nacional de Proteção de Dados*). It is also noted the existence of Ethics Committee for Health (CES - *Comissão de Ética para a Saúde*) that play an active role in the approval circuit at the level of institutions and, by explicit delegation could even take on the role of CEIC.

The involvement of so many stakeholders of different specialties is one of the reasons why implementing and working with clinical trials requires expertise, training and experience. It requires knowledge of the regulatory framework which varies between countries. It requires a multidisciplinary team trained in clinical trials. Besides the stakeholders, the setting up and running a clinical trial involve several phases since the ethical issues to the follow-up of the participants.

After getting all the ethical and legal authorization the study can start in the selected centers. The centers are not chosen at random. A number of potential centers where the clinical trial could be held are selected by the sponsor to check if they are feasible to conduct the trial. Then, the feasibility process occurs. The objective of a feasibility process is to evaluate the adequacy of the site, the training and experience of the study staff, the access to the right patient population, and

the site's interest in the study. If a center meets the needed requirements to conduct the trial and shows interest in conducting it, the feasibility evaluation is complete and the center is eligible to enter the trial.

The study starts with the initiation visit. In the initiation visit the sponsor or the team by him delegated goes to the respective centers and explains the procedures to the clinical trial team, in order to answer or clarify any question.

Next comes the recruitment, which is done in the pre-screening visits. Where a physician of the team will explain the trial performed to a potential participant who receives a copy of the informed consent to be read carefully. The IC is a nuclear document in clinical research. The concept of consent ascends from the ethical principle of patient autonomy and basic human rights (20). Patient's has all the freedom to decide what should or should not happen to his/her body and to gather information before undergoing a test/procedure/surgery. There is also a legal angle to this concept. As no one has the right to decide alone to treat another person. Any such act, done without permission, is classified as "battery"- physical assault and is punishable. Hence, obtaining consent is a must for anything other than a routine physical examination. Therefore, the IC is not only an ethical obligation, but also a legal urge (20). This document aims to protect patient's autonomy, and ensure their well-being. The information disclosed should include:

- The condition/disorder/disease that the patient is having/suffering from
- Necessity for further testing
- Natural course of the condition and possible complications
- Consequences of non-treatment
- Treatment options available
- Potential risks and benefits of treatment options
- Duration and approximate cost of treatment
- Expected outcome
- Follow-up required

After discussing, analyzing and see all doubts clarified the information provided about the clinical trial, if the patient decides to participate in the study, it has to sign the IC in the presence of the PI. Next comes the screening visit, it 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' randomization (if required in the research protocol) and the appropriate distribution of medication. During this period the

participant will need to visit the center for medical appointments and to collect the necessary clinical data, according with the timeline and the requirements defined in the research protocol. Checking patient's compliance with the trial's procedures, health status, drug accountability, and many other procedures usually happen in these appointments. During this phase the sponsor has the responsibility to monitor the study in order to ensure the rights and well-being of participants. The sponsor has, also, 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. Normally, this task is delegated to the study monitor as aforementioned.

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. Open-label extension studies are an opportunity for the patient to receive the experimental drug without the blinding, this represents even more benefit for patients who were randomized to placebo.

It is important to note that not all the patients will reach the end of the study. As stated in the IC form, the patient is free to leave the trial anytime. In other cases, the principal investigator (PI) may have to terminate their participation earlier because he might no longer fit the inclusion or exclusion criteria, or might have violated any of his duties stated in the IC as for example, take prohibited medication alongside the experimental treatment. An adverse event might occur while taking the experimental medication or a female participant might become pregnant.

2.1.3. Ethics and legal authorisations

To perform a clinical trial in Portugal it is necessary to obtain an authorisation from the INFARMED, an ethical opinion from the Portuguese Ethics Committee for Clinical Research (*CEIC)* and an approval from the National Data Protection Authority (*CNPD)*.

With the introduction of the latest clinical research law - Law No 73/2015 of July 27th (17) – it was also created an electronic platform, named as the National Register of Clinical Trials (RNEC – *Registo Nacional de Estudos Clínicos)*. This platform is used for the online submission of all the applications for clinical trials/studies. It was developed to promote the interaction between the different stakeholders in clinical research and to simplify and boost 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 (16). Although its great potential to bring together all the

information about current Clinical research in Portugal, it is not yet running this platform. So the applications to clinical trials must be submitted in paper format and in CD-ROM.

There are many information and necessary documents to submit an application to the authorities for example: application form; clinical research protocol; protocol synopsis; information about the sponsor, investigator-coordinator, and the PI; investigator's brochure; data about the investigational medicinal product; And many others.

Some of the required documents to submit a clinical trial to INFARMED and CEIC must be in Portuguese or English, such as the protocol and synopsis, case report form (CRF) and informed consent. When these documents are in another language they must be translated.

A clinical trial protocol is the document that defines how the clinical trial must be conducted, and it aims to guarantee the safety of participants and the reliability of the obtained 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 organizations; and references of the literature (21).

A CRF is a form filled by the physician for each participant in the study. This document should be study protocol driven, robust in content and have material to collect the study specific data (22). The CRF development objectives are preserving and maintaining quality and integrity of data. CRF design should be standardized to address the needs of all users such as investigator, site coordinator, study monitor, data entry personnel, medical coder and statistician (22). It can be electronic CRF (eCRF) or paper CRF. The collected data usually 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.

2.1.4. State of clinical trials in Europe and in Portugal

In order to compare Portugal with other countries we used the gross national product (GNP) values to determine which European countries to compare. According to data from the world bank (23), the European countries with the closest GNP per capita of Portugal (19526€) are Slovenia (21555€), Czech Republic (16793€), Greece (20733€) and Estonia (17396€) while countries like France (39272 €), Germany (43550€), United Kingdom (39701€) and Spain (26912€) have a higher GNP. The figure

below (Figure 1) represents the approximate number of clinical trials ongoing in 2015, for the countries aforementioned, retrieved from the European Union Clinical Trials Register (EUCTR). The EUCTR allows the research for protocol and results information on interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA). In its turn the ECTRU gets the data from the database EudraCT which is the database used by national medicines regulators for data related to clinical trial protocols. The data on the results of these trials are entered into the database by the sponsors themselves (24).

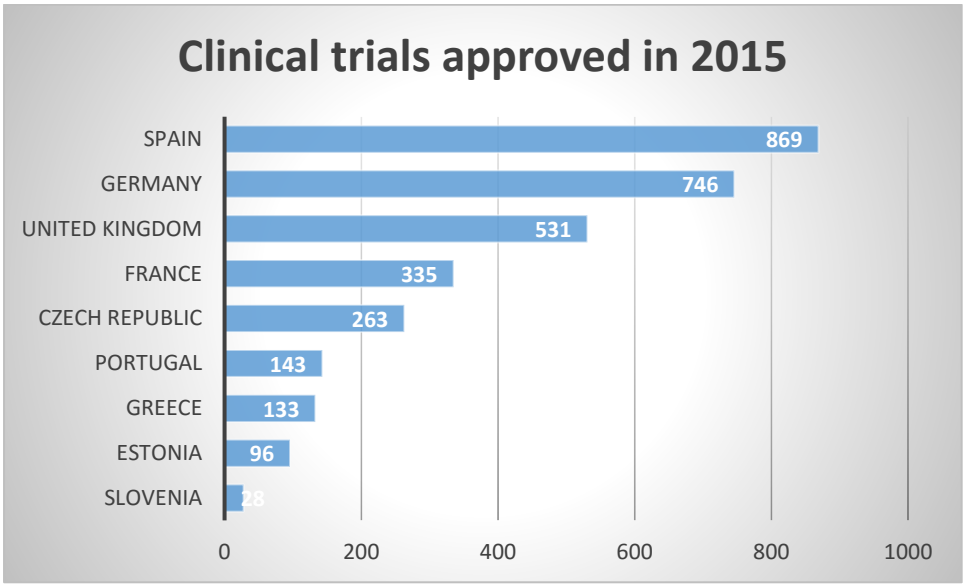


Figure 1 Clinical trials approved in the EU for 2015 [adapted from: EU Clinical Trials Register; **accessed date**: 02-Feb-2016**]**

As we can see in the Figure 1 Portugal does not have very disparate values of the countries with a GNP equal to his, but falls short of the research output of the largest economic and scientific potencies of Europe, who have more than three times the clinical trials by year. According to data from INFARMED (25) in 2014 Portugal saw only 127 trials being submitted for approval, 114 in 2013 and 118 in 2012 (26). This highlights the stagnation in research, especially in terms of clinical trials that Portugal is going through. Around 2011/2012 the main factors to the declination of clinical trials in Portugal were the weak capacity of patient recruitment and the complexity of legal procedures and consequently the approval time becomes too long resulting in loss of competitiveness (27). A study carried by APIFARMA (*Associação Portuguesa da Indústria Farmacêutica*) calculated the total investment planned for the patients included and the total investment for patients actually enrolled in clinical trials between 2007 and 2011. These values as

well as the estimated loss for patients not recruited are shown in **Erro! A origem da referência não foi encontrada.** (28). As we can see, there's an estimate of 8.993.427 € loss due to weak recruitment. In order to improve clinical trials in Portugal, APIFARMA at that time proposed measures such as creation of dedicated management structures for clinical research, improvement of conditions for Clinical Trials in Primary Care and adaptation of health professionals career and work schedule to clinical research (19, 27).

Therapeutic areas	No of Studies	Mean investment /participant (€)	No. planned participants	No. of participants enrolled	Total planed investment (€)	Total invested (€)	Investment loss (€)
Cardiology	75	5.997	787	440	4.719.639	2.638.680	2.080.959
Infectiology	44	20.749	186	173	3.859.314	3.589.577	269.737
Neurology	54	10.928	753	421	8.228.784	4.600.688	3.628.096
Oncology	50	31.733	276	181	8.758.308	5.743.673	3.014.632
Total	223	69.407	2.002	555	25.566.045	16.572.618	8.993.427

Table 1 - Resume of the investment by patient enrolled in clinical trials between 2007 and 2011 [adapted from: *Jesus PMd. 2012*]

With the introduction of the Clinical Investigation Law (n.º21/2014) (16) the objective was to improve clinical research in Portugal. Decrease the authorization timelines, establish a CEIC coordinated Ethics Committee networking. These measures resulted in a small improvement in the number of clinical trials submitted to Portugal. According to INFARMED data (25, 26) in 2014 were submitted 127 trials, 13 more than in 2013, and in 2015 were submitted 137 trials 10 more than in 2014. And in 2014 the average assessment time for clinical trials was 33 days, 13% lower than 2013. Although the law has introduced changes in the national scene particularly in terms of approval by the INFARMED there are other parties who are not so covered by law and so have some flaws that may prejudice the evolution of clinical research in Portugal. For example, CNPD has a deadline of 30 days to rule on a particular study. In one of the observational studies that I worked on during the internship the CNPD took 6 months (approximately 180 days) to pronounce about the study which hampered the study and could have even prevented the same due to such delay. Although it is only an observational study and not a clinical trial itself, this represents the delay in the approval/opinion of clinical investigation. Delay that may undermine the achievement of the same. As a personal opinion and recurrent from the experience acquired with the internship I think that the reason that in Portugal the number of clinical trials aren't greater is because of a problem in the recruitment phase. It's extremely difficult to recruit patients to a study, sometimes because they don't meet all the criteria, sometimes because the Portuguese people still have a misconception about clinical trials and don't see the real advantages of it. In other hand the mind-set of the doctors is not directed to clinical trials and only to the standard practise of medicine.

2.2. What is medical writing?

Before entering the field of systematic reviews and meta-analysis is to better explain what is Evidence-based medicine (EBM). EBM is an approach to medical practice intended to delivery of best clinical care to patients by emphasizing the use of evidence from well designed and conducted research (e.g. meta-analyses, systematic reviews and RCTs) (29). Sometimes an RCT may fail to give a clear outcome, or results from multiple studies may yield different estimates of treatment effect. In this cases systematic review and meta-analysis could solve the problem. Doing a systematic review one would identify and join all published information in a given clinical area (e.g. diabetes) and with a meta-analysis pool the results in a statistically valid way.

High quality systematic reviews seek to (30): Identify all relevant published and unpublished evidence; Gather studies or reports for inclusion; Assess the quality of each selected study or report; Synthesize the findings from individual studies or reports in an unbiased way; Interpret the

findings and present a balanced and impartial summary of the findings with due consideration of any flaws in the evidence.

Medical writing involves writing scientific documents of different types which include regulatory and research-related documents, disease or drug-related educational and promotional literature, publication articles like journal, manuscripts and abstracts and content for healthcare websites, health-related magazines or news articles (31).

The type of language used and the development of concepts is adjusted according to the target audience (patients, general public, physicians or regulators). Hence, more than having the scientific knowledge of medical terminology and concepts, ethical and legal issues, guidelines for the structure of specific documents, managing and presenting clinical data, it is important to have a set of skills related to the act of writing itself. Because sometimes the professional concepts must be presented to the most graduated doctor or to a common patient without any type of literacy (31).

The first step in medical writing is understanding the purpose and the goals to achieve with the document to be written. Next is good to search literature and review of information, to support the document writing. After this, a draft is written, this part is the most consuming since it requires familiarity with the type of document, its purpose and contents. The review of contents and editorial/ formatting review comes next. The former is usually carried out by a more experienced medical writer and a subject matter expert who verify if the document has the legal required format, if all the data is true and trustworthy. Quality check of contents involving cross-checking all verifiable information with the source data is also a must. Upon finishing the content review it's time to formatting (checking text font and size consistency, line and paragraph spacing, headers and footers, margins, page numbers, etc.) and editing (language, spellings, punctuation marks, correct use of tense, appropriate reference style, etc.). Documents that are required for publication or electronic publishing need to be rigorously copy-edited, proof-read, and checked for formatting requirements (31). The final step regards the document publishing or release, made by an expert after the approval of the final manuscript. Medical Writing is important because is a way of sharing new data, which is encouraged in order to provide new knowledge to researchers, sponsors, scientific community and general public.

2.3. What is pharmacovigilance?

One of the downsides of drugs are their possible adverse effects. According to ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A the definitions are (32):

- Adverse Event (AE) or Adverse Experience – Any inconvenient medical finding in a patient administered a pharmaceutical product, whether or not considered causal related to the medicinal product
- Adverse Drug Reaction (ADR) – For pre-approval clinical experience, all harmful and unintended responses that are causally related to the medicinal product, no matter the dose should be considered adverse drug reactions. While for marketed authorized medicinal products, an ADR its only considered when it the harmful and unintended responses occur at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
- Serious Adverse Event (SAE) – This is a classification given to ADR or AE. A serious adverse event or reaction is any inconvenient medical occurrence that at any dose results in any of this outcomes: death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect.

By the definition of World Health Organization (WHO) Pharmacovigilance (PV) is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” (33). The pharmacovigilance studies have as principal objective to gather information about the drug’s safety, especially in his post-marketing phase. The drugs reach commercialization, supported on safety data from clinical trials, which as a whole, usually involve a few thousand patients. These actual may, however, not be sufficient to demonstrate some adverse events that occur 1/10000 or lower rates. On the other hand, the fact of the populations studied are often selected on the basis of strict inclusion and exclusion criteria, may lead to the safety information collected during the clinical phase of testing does not reflect the specific characteristics of the population that will "consume" this medicine (34). Regulators have to strike a balance between making new medicines available for use in patients as early as possible and waiting until sufficient information on a product's quality, safety and efficacy is known. For that reason, the systems of pharmacovigilance are of extreme importance. By continuing to collect information on the medicine after it has been authorized to be placed on the market and taking action in response, regulators can continue to protect the public from emergent safety issues throughout a medicine's life cycle, thereby certifying its safe and effective use.

The most remarkable event in pharmacovigilance history dates back to late 1950s. Thalidomide was marketed as a very safe medicine in Europe, Australia and Japan, based on the available clinical data. Prescribed at first as sedative and hypnotic and, subsequently, used by pregnant women

against nausea and to relieve morning sickness (35). Until the early 1960s when started to note severe congenital malformations in more than 10,000 children, phocomelia (malformation of limbs), amelia (absence of limbs), congenital heart disease and also deformities in ears, eyes, heart and gastrointestinal system (35). 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. It is currently used as treatment of leprosy and multiple myeloma (36). As a result of the thalidomide tragedy, the resulting lessons were learned (35):

- Pharmaceutical products must be tested to evaluate long time effects before marketing.
- It's important to use different species (The closest possible from human species) in drug testing.
- When the point above is not possible there must be a more robust testing and interpretation of results in a single species.
- The importance of Pharmacovigilance systems.

So in 1968, in order to identify ADRs that could not be found through clinical trial programmes it was created the *International Program of Adverse Reaction Monitoring* by WHO (37). With the evolution and expansion of the drug safety monitoring very important Regulatory Entities and Organisations aroused.

Nowadays there are several entities and organizations that have a major impact in Pharmacovigilance. The most important in Europe is the European Medicines Agency (EMA) is a decentralised agency of the European Union, its principal responsibility is to guard and promote public and animal health, through the evaluation and supervision of medicines for human and veterinary use (38). What concerns to safety monitoring specifically the agency is responsible for coordinating the EU's safety-monitoring or 'pharmacovigilance' system for medicines. It monitors the safety of medicines through the EU network takes action if information shows that the benefit-risk balance of a medicine has changed since it was authorised. The EMA has a Pharmacovigilance Risk Assessment Committee (PRAC), which provides recommendations on the safety of human medicines. The Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party deal with safety issues for veterinary medicines. The EMA is also in control of the development and maintenance of EudraVigilance and EudraVigilance Veterinary, the EU reporting and data-storage systems for side-effect reports, and for supporting signal-identification activities in the EU, including coordinating the EU rapid-alert and incident-management systems for responses to new safety data. (38).

In Portugal, INFARMED and it is the Department of Medicine Risk Management are responsible to ensure the functioning of the National Pharmacovigilance System, more accurately, is responsible to collect, assess, and disclose the information about suspected ADRs. The actual National Pharmacovigilance System is divided in Regional Pharmacovigilance Units (RPU). 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 Lisbon and *Tejo* Valley Regional Pharmacovigilance. The last where I spent 2 months of my internship.

Task Name	Start Date	End Date	Duration
Clinical trials	09/14/15	11/13/15	45d
Medical writing/Statistics	11/16/15	01/08/16	40d
Project Manager	01/11/16	03/11/16	45d
Pharmacovigilance	03/14/16	05/04/16	38d
Clinical trials	05/09/16	06/30/16	39d

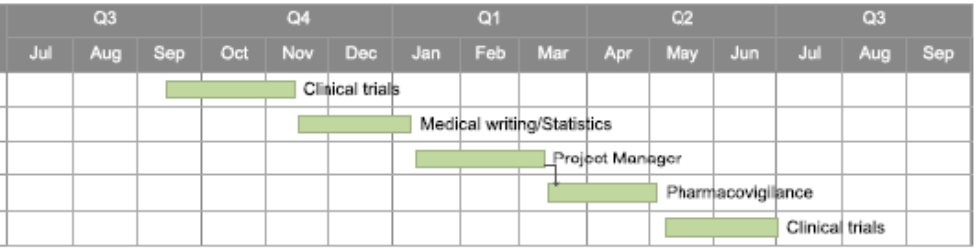


Figure 2 - Gantt chart of my internship

3. Developed activities

My activities can be divided in three main topics: clinical trial coordination, medical writing and pharmacovigilance.

Clinical coordination was held in the NCRU, I had the responsibility to coordinate some of the studies taking place there. They were PROTEC, EPOCH, ENGAGE, ORATÓRIO and PROTEC. Medical writing and pharmacovigilance took place at Laboratory of Clinical Pharmacology and Therapeutics (LCPT). In this part I worked in some systematic reviews, managed an observational study and an assembling application of a TASK FORCE. At pharmacovigilance I participated in the processing of notifications and of possible alert signs. All this will be reported in more detail in the following sections.

Figure 2 shows the chronogram of the active ties that I performed in my internship.

3.1. Clinical trials

My time in clinical trials was divided in two separate periods. The first initiated in September and ended in mid-November, and the second started in May and finished at the end of June. There were some differences between the two periods. In the first period I worked in almost all the studies while in the second period I was allocated to specific studies.

The specific studies that I was allocated at where:

- PROTEC – A phase IV study of an approved medicine to multiple sclerosis.
- EPOCH – A phase III, randomized, placebo controlled, parallel group, double blind study in subjects with mild to moderate Alzheimer.
- ENGAGE – A phase III, multicentre, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy of a specific drug in early Alzheimer.
- ORATÓRIO – A phase III, multicentre, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of a specific drug in adults with primary progressive multiple sclerosis.
- EXPAND – A phase III, multicentre, randomized, double-blind, parallel-group, placebo controlled variable treatment duration study evaluating the efficacy and safety of a drug in patients with secondary progressive multiple sclerosis.

In the NCRU, I worked under the close guidance of Dra. Ana Noronha and Dra. Ana Salgueiro, and alongside my colleagues from the master's, Nádia Lourenço and Raquel Rodrigues. I initiated my internship at a time when the NCRU and its coordinators were very occupied with work. Consequently, my presence was appreciated. The first week of the internship I received training

from Dr. Ana Noronha and Dr. Ana Salgueiro. I received a full impression of the clinical trial site, the procedures in place, where the material was stored, and the general workflow of the center. Since I was in a completely new environment, in this initial week, I spent the majority of the first week asking questions related to the procedures, and receiving important feedback on my work. I started by reading the protocols of some of the studies I would work in, to get used to the respective procedures, and to ensure that I would comply with the investigation so that the results collected during the trial are accurate and scientifically rigorous. Once I had shown to understand the protocols of the studies, I was able to collaborate in the visit procedures of the several clinical trials. In the next sections I will describe some of the specific task that I have done.

3.1.1. Preparing the subject's visit

Once a subject is enrolled in a study I must do schedule visits defined by the protocol. An appointment is made with the patient and that visit must be prepared in advance; this is a work done by the clinical trial coordinator. Usually, it is the responsibility of the coordinator to schedule visits, and prepare these visits in advance, so that nothing fails in the day of the visit. The preparation may involve identification of collection tubes, schedule of extra-center tests such as x-rays, computed tomography, positron emission tomography or schedule of transportation to the patients with the firefighters or taxi services. The informed consent must be available (when It's a pre-screening visit or when there an amendment to the original protocol) as well as all the others document that are needed for this visit as for example evaluation scales like Clinical Dementia Rating (CDR) or Columbia Suicide Severity Rating Scale (C-SSRS). Each visit has a set of evaluations to do.

Before each patient appointment, I had to study the core assessments of the visit, and the previous visits and history of the patient. Each appointment was scheduled by phone a few days before it, and in that phone call when applicable I was responsible to remind the patient to come fasted, bring the rest of the study medication or to bring his patient diary. A day before the visit, I took all the necessary material for the visit from the study cabinet, like the patient's medical file, the source documentation, Interactive Voice Response System **(**IVRS) or Interactive Web-Response System (IWRS) sheets, vital sign form and pharmacy prescription forms. I also prepared the laboratory tubes, pre-labelling them with the patient's identification.

3.1.2. Measurements and vital signs

The protocol defines what measurements are necessary for the study. Weigh, measure body temperature, the blood pressure, heart rate and respiratory rate are probably elements required

in any study visit. This are tasks that a clinical trial coordinator can do, and that spares time to the principal investigator. After some initial training with Dr. Ana Salgueiro I was able to do it all by myself.

3.1.3. Processing of laboratory samples

Each study had a laboratory manual with instructions on how to collect, handle, process, and ship the required biological samples for each visit. Bio fluids such as blood or urine, and their derivatives, are important resources for biomedical research, as they provide very important data about safety and efficacy during the conduct of a trial (39). At NCRU we collected only blood and urine are collected. My job as a clinical trial coordinator trainee was to centrifuge the required samples according to the laboratory manual and prepare each sample to be shipped to the responsible laboratory which vary according the study. They can be shipped either in ambient temperature or in dry ice.

3.1.4. CRFs and e-CRFs

In each visit the principal investigator or a specific physician of the research team who perform an evaluation on the subject have to fill a CRF. Those CRFs then have to be transcribed in full to the e-CRFs. E-CRFs are an electronic data collection tool provided by the clinical trial sponsor for the center to collect data on the trial they are nothing less than an electronical representations of the paper CRF. In my internship I had to learn how to handle different types of trial specific e-CRFs, which vary in layout, design and specifications. The first few times were made with monitoring and training of Dr. Ana Noronha and Dr. Ana Salgueiro. Most of the CRFs are confusing at first, especially the older ones, this task requires technical and scientific accuracy. Once made a mistake in completing this document, a query will be soon lifted. A query is a question which appears automatically if anything is made contradictorily to the CRF rules or if any information is inconsistent or contradictory. Throughout the internship, there were many queries that required quick resolution. From simple queries, like data entry errors which were easy to resolve, to more complex ones, like the ones related to inconsistences or incoherencies in evaluations and procedures that required a team effort amongst physicians and coordinators to be solved. The importance of data confidentiality when accessing the different e-CRFs was also made clear during the initial training. After finishing a visit, I reviewed all source documents, to make sure that all necessary data was collected, and then proceeded to enter it on the e-CRF. All material used was filed correctly on the patient's folder.

3.1.5. Archiving

Archiving is an important step in CTs. Something that is not written was not done, because there's no proof. As defined in the *Commission Directive 2005/28/EC of 8 April (40)*, *"the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion."*, they also have to be archived in a way that makes then readily available, upon request, to the competent authorities. Essential documents should be complete, comprehensible, truthful, and unequivocal. They should be signed and dated as appropriate. Each study has a cabinet with the dossiers, where all documentation of a clinical trial participant is kept, the investigator site file, which include the study protocol, contact information, financial agreements, study manuals, and much more. One of my responsibilities was to archive all the documents of the studies that I was in charge, from a paper CRF to a laboratory shipment confirmation. All should be kept organized, in place, and readily available. Losing any of this document means losing important information.

3.2. Systematic reviews and data management

During my internship I developed a systematic review of the European Society of Cardiology ESC Clinical Practice Guidelines with Dr. Daniel Caldeira. Of the ESC Clinical Practice Guidelines list we identified the guidelines related to disease management and procedures from 2009 and forward. The identified guidelines were collected along with their most previous version. From the gathered guidelines I abstracted all the recommendations and their class and level of evidence to a data base. The class and level of evidence of the recommendations is a system to classify them reliability and evidence that supports it. That said, any guideline which does not presented the recommendations with class and level of evidence was not selected for this analysis. These recommendations are normally displayed statements in tables across the document and are distinctively separated from the current text. Each recommendation has a class and level of evidence that are inherent. Therefore, data collection performed only reflected the contents of the documents, the guidelines, and was not the subject of any judgment by us, abstractors. The objective of this analysis was to describe the distribution of recommendations by classes and levels of evidence. For guidelines included with a previous version was also made an assessment of the evolution of that distribution between the current and the previous versions.

The result of this systematic review was mainly a descriptive analysis of the distribution of the recommendations and its classes and levels of evidence from which we concluded that recommendations issued in current ESC disease-based guidelines are largely developed from lower

levels of evidence or expert opinion. The expansion of evidence-based data from which clinical practice guidelines are derived is required.

To this systematic review doing a meta-analysis was not applicable because the objective was not to integrate the results of different studies. So using the descriptive analysis, myself and Dr. Daniel Caldeira prepared a paper which was later accepted to be presented at the Congress of the European Society of Cardiology 2016 that occurs at the end of August in Rome.

I also developed a systematic review with subsequent meta-analysis with Raquel Rodrigues under the guidance of Dr. Daniel Caldeira on the influence of caffeine consumption in the risk of Cardiovascular Diseases (CVD) in patients with previous myocardial infarction.

First of all, a protocol was made based on the Review manager (RevMan) model. In the protocol the objectives and methods of this review were defined. In order to perform a systematic review and meta-analysis on this subject there was a need to gather studies that addressed it.

The investigators team retrieved potential eligible studies through an electronic search in PubMed MEDLINE, CENTRAL and EMBASE, from inception to December 2015. The search strategy for PubMed included free-text words and MeSH (Medical Subject Headings) terms without language restrictions. Some of the key words were: coffee, caffeine, risk, cardiovascular diseases, cardiovascular events, myocardial infarction, clinical trials etc.

As criteria for inclusion in the review were considered eligible all randomized controlled trials and prospective or retrospective observational studies evaluating exposure to caffeine (as coffee component) and risk of major adverse cardiac events (MACE) in patients with previous history of myocardial infarction MI (STEMI or NSTEMI). Studies addressing the effects of short-term exposure to caffeine (ie, <6 months) as well as studies evaluating caffeine exposure in patients who had not prior MI were excluded. Studies that met inclusion criteria were not excluded a priori on the basis of weakness of design or data quality.

The search done resulted in 528 articles found and uploaded to covidence. Titles and abstracts of obtained articles were screened by three authors (João Almeida, Raquel Rodrigues and Dr. Daniel Caldeira). Any disagreements between reviewers were solved through consensus. 503 articles were excluded in this first screening. The other 25 selected studies were assessed in full-text to determine their appropriateness for inclusion. 10 were selected and submitted to a risk of bias assessment.

It was used a five-item classification system based on MOOSE (41), QATSO (42) and STROBE (43) adapted from previous published quality assessment instruments.

The following items were taken into consideration:

- Participants, if the population was adequate and the study reported appropriate inclusion and exclusion criteria;
- Exposure, if caffeine exposure use was adequately assessed through food questionnaires;
- Outcome, if MACE was assessed by clinical, ECG methods or through database codes, and not exclusively based on self-report;
- Specific outcome adjustments, for both age, sex and at least one of cardiovascular disease (MI), alcohol intake or smoking;

After a proper risk of bias assessment, the characteristics and results were extracted independently by three authors into a standardised form. Investigators also extracted the following variables: population characteristics, region of study, study follow-up, caffeine exposure assessment, reference category, outcome assessment, outcome adjustments. At the time this thesis was written this review is to wait two articles found a posteriori and is awaiting the phase of statistical analysis.

3.3. Project Manager and Medical writing

During my internship I was able to work has a project manager for Professor Ricardo Fernandes. Professor Ricardo Fernandes is a paediatrician at the department of Paediatrics of the Hospital de Santa Maria. He was principal investigator of *"Projeto ALFABETO: Alto Fluxo – Antever na Bronquiolite a Eficácia Terapêutica e Outcomes"*. An observational study which the primary objective was to identify factors of demographic prognosis, clinical and physiological success / failure of the oxygen therapy high flow administered by nasal cannula (OHFNC) in acute bronchiolitis. And as secondary objectives the study was designed to compare the usability of OHFNC for health professionals in acute bronchiolitis in different environments / hospital care levels and to evaluate in an exploratory way the efficacy and safety of OAFCN in bronchiolitis clinical / physiological parameters, and global assessments reported by health professionals and parents / caregivers.

My function as an intern in this study was to act as both a project manager and a study monitor. As a project manager I was responsible for create all source documents for the various centers involved in the study, for example the informed consent and the paper CRF. I was also accountable for contacting each center when there was a need to spread a newsletter or to apply an addendum to the protocol. My tasks as study monitor were to transfer information from the paper CRF for electronic database, review information of the paper CRF and lift queries where necessary. Basically

I should ensure that the information collected by the centers was always in accordance with the protocol and not violating the rights of participants.

During my time with Professor Ricardo I also participated in preparing a proposal for an European Respiratory society (ERS) Task Force. The ERS Task Forces are ad hoc groups set up to address a specific issue in respiratory medicine. Its objective is to produce position papers, statements or clinical practice guidelines that then are adopted as official ERS documents on issues related to respiratory medicine (44). The title of the proposed task force was "Standardizing definitions and outcome measures in acute bronchiolitis", this involved many experts in the paediatric and respiratory fields, and their objectives was to provide evidence-based guidance on bronchiolitis definitions, and selection of outcome measures in future studies.

My responsibility was to gather all the important data for the proposal. For example, the ERS conflict of interest and confidentiality agreement form dully filled by each off the participants.

3.4. Pharmacovigilance

This phase of the internship started in 14th March of 2016. The first two weeks were of introduction, knowledge and familiarization with the UFLVT unit and its procedures.

At the first day, Dr. Ana Marta Anes gave me an explanation about the pharmacovigilance area, the unit's work and some of its objectives. The following week and a half I read some chapters of the book *Farmacovigilância em Portugal (34)* about historical aspects of pharmacovigilance, legal and regulatory framework and the organization of the National Pharmacovigilance System. I complemented this reading with the contracted agreement between INFARMED and UFLVT in order to understand the specific role of the UFLVT in the national pharmacovigilance framework and the objectives that need to be accomplished in order to fully meet the contract numbers.

Once I understood the role of UFLVT I started to review the Quality Management System (QMS) documents (quality manual, processes, procedures, work instructions, document models, and records). This allowed me to know the standard procedures of the unit, its organization and the way that all the developed work is kept and controlled. But also to get in touch with some of the previous ADR reports preparing me for what was to come. The revision of the older ADR reports was also accompanied with the above mentioned book (34) which as the description of many of the Adverse reaction that are usually reported to the unit.

After this initial training I was able, at some extension, to start to collaborate in the daily activities of UFLVT. I was introduced to treatment procedure of a spontaneous notification of an ADR and I processed one or two myself.

A spontaneous notification of and ADR can arrive by e-mail, telephone, fax or mail. In order to be fully assessed and considered as valid it must have the minimum requirements:

- identification about the notifier (currently, any person can report an ADR);
- Some identification about the patient (Example: Sex, age, name initials. The patient should not be identified with personal information as tax identification number and others)
- Active substance;
- Signal or symptom of an ADR.

When the notification is received it will be dated and signed by the receiver.

Next the case is added to the SVIG, a database of the Pharmacovigilance National System, and attached with a copy of the original report provided by the notifier. This data entry is later communicated to the Pharmacovigilance department of INFARMED. As soon as this data is sent to SVIG the system generates a number which functions as a unique identifier of the ADR report.

A reply is also sent to the notifier with the confirmation of data reception and acceptance of the report and with a form asking for additional information in order to have the most complete ADR report possible.

Later the medical coordinator of the unit must judge the notification through the analysis of the Summary of Product Characteristics (SPC) and the Periodic safety update reports (PSUR) of the drug, in order to assign the proper causality category, which is posteriorly included in the SVIG.

Once this causality evaluation is finished, causality category is then used to prepare a causality report and letter. One of my tasks was to prepare those reports and letters. Using a premade form, my responsibility was to adapt the form with the specific information of each ADR. At the same time, I studied the ADR reports and realizing the most frequent reactions to certain types of drugs. The causality letter is intended to be sent to the notifier and the causality report is intended to be attached to the SVIG.

Along with causality letters and reports each ADR report must also have a narrative, which is a description of the actual report received by the UFLVT. At a certain time point in my internship I was also responsible to do the narratives of the ADR reports coming in. Making this narrative implied knowing and understanding the history of the ADR, the suspected drug taken, the reaction triggered, the concomitant medication, the treatment of the reaction, the time intervals and all actions taken relating to the reaction, such as suspension of the drug or dosage reduction. All this information was then written in the narrative form chronologically.

For realizing all the tasks aforementioned I used a very important tool in pharmacovigilance, the MedDRA dictionary which is a rich and highly specific standardised medical terminology developed

by ICH to facilitate sharing of regulatory information internationally for medical products used by humans (45).

The internship ended at 6th of May of 2016 and by this time I was able to fully understand the temporal, clinical evolution and the mechanisms compatible with an ADR. I also recognize that pharmacovigilance is essential to a better and safer use of the available market drugs and that UFLVT plays a key role in pharmacovigilance in our national pharmacovigilance system.

3.5. Other activities

3.5.1. Training session about the Instituto de Medicina Molecular

The day one of my internship, started with a training session related to the IMM. A theoretical session which had as objective present the institution objectives, hierarchy, sectors, projects under development and modus operandi. It also involved a field visit to the facilities of the IMM, laboratories and scientific equipment rooms.

3.5.2. Wednesday Meetings

On Wednesday of every week there was a meeting at 8 am at NCRU which involved the staff of the unit. Mostly physicians that were individually assigned to each Wednesday to present a clinical case or a recent study of impact on medical practice.

Fortnightly, at the end of the day, 6 pm on Wednesday, the members of all the CPU sub-units and other collaborators gather in a meeting room with the objective of sharing and discussing on-going and future projects. For each meeting a specific collaborator was selected to do an oral presentation about his work. At the end of this presentation there was room for discussion with the audience. The purpose of these meeting was to keep all the staff up-to-date about the recent projects, new developments and future plans, and also to improve each work as possible. Once the discussion was generated by the multidisciplinary team of CPU it provided diverse feedback, opinions and new ideas and views of the project to its leaders.

4. Discussion

The internship documented in this report was mostly comprised of working in coordination clinical trials at NCRU, and also involving other departments and fields of work. It was an internship which gave me the opportunity to contact with different areas related to Clinical Research and realise how they work together with a shared goal. Although it is very difficult to properly describe all the effects of this on-the-job training in my personal and professional life, in the following paragraphs I will try to describe the impact that it had in development as a person and as a professional.

I was privileged to work so closely in clinical trials at NCRU. Working in clinical trials at a research center is different than work in a CRO that also works in clinical trials. While working in a CRO involves more of a back office work guarantying that the CT is carried within the country and European laws and accordingly to the protocol. Working in a clinical trial facility implies that and more of human effort. Working at NCRU gave the opportunity to have a closer experience with the patients, work with the hospital pharmacy staff, process biological samples. Activities that I wouldn't be able to develop at a CRO. A study coordinator in Clinical trials must have the scientific knowledge necessary to accomplish all the legal framework, to follow the protocol and to deal with any type of circumstance that may force a protocol deviation. Having the know how to face the problems of implementation and development of a CT is very important. This knowhow I acquired during my master's degree. I was taught, as a universal law of clinical trials, that the safety and well-being of the subjects of clinical trials is the first and foremost. So that integrity and privacy must be respected and guaranteed and harm must not be done in any case. The know how is necessary, but the sensibility to realize that in a CT we are dealing with human life is very important. This was a skill that I developed a lot during the stage because in a CT there is a normal variety of people who have some type of pathology and due to that may be more fragile individuals, may have more fragile families and may live in a more fragile setting. Being a study coordinator is being able to deal with all this conditions. Because we, the study coordinators at NCRU, spent as much time with the patient as the physicians and unlike physicians, they see us as closer people they open up to us. And when that happens we must know how to deal and interact with each one of the subjects.

Almost our patients have a neurological disorder and the approach should be more careful. The way that they react to their own pathology is different and that conditions the way we approach, because there are different types of individuals with different pathologies and different stages. For example, there are those individuals in denial that almost reject being treated and with those it is almost impossible and unthinkable to talk about the pathology, the treatment or anything related

to it. Here the choice is to speak with some close family or with their caregiver when there's one. In order to follow the patient status, on the other hand, I had to deal with patients that fully understand and "accept" their condition. With these we can talk about their life in day by day, ask about life problems and find if there´s something where we can help outside of clinical trials. It´s important to talk about the development of their participation in clinical trials or even to inform them about any progress related to their pathology.

Working as a study coordinator at NCRU compelled me to develop my inter-social and organizational skills, also my sense about some of real problems like Alzheimer or Parkinson diseases in a closer, more human and less medical, perspective. It gave me the capacity to value more my surroundings. Aside this human growth the clinical coordination also allowed me to develop professional skills. Due to the fact that in a trial there are many different people involved, for example principal investigator, assistant physician, physiotherapists and psychologists, the patient itself, the monitors or sponsors. It is difficult sometimes to deal with all the stakeholders involved and organize the visits depending on their schedules. That made me develop my organizational skills and to learn to be flexible. Even more because I had not one, but five clinical trials to my charge. The first weeks were a little agitated because there were many different names to memorize, and associate to their functions and respective trials. At this stage the help of Dr. Ana Noronha and Dr. Ana Salgueiro was more important than ever. Because every time I couldn't remember who to contact or who were contacting me they guided me. Many times I had more than one visit per day from patients of different studies. When this happened, I had to be really organized because it was necessary to request different medication to the pharmacy, prepare specific rating scales for each visit and warn the respective doctors and evaluators. While the patients were evaluated by the medical staff I had to process all their biological samples which had specific timings. In order to comply with this timings, I often had to rely on the help of other staff to do the processing phase so I could receive medication and deliver them to the patient or even to help the medical staff doing something. This was also a skill that I could improve, my ability to teamwork. I was helped and I also helped the other members of the NCRU when they were busy and I had more free time.

My pharmacovigilance time contribute a lot to understand its importance in the real world. There I learnt more about medicines and about what's more used in our country. Some insights that I got was that users notify more adverse events that affect them at the day-by-day life, because over 50% of notifications processed by me were with regard to the severity criterion classified as *"resulted in an inability to perform daily tasks"* by the users. I also realized that each time Dra Ana

Marta held a lecture on the pharmacovigilance system and notifications in a particular service there was a slight peak of notifications in the following days by that service.

Although I already had the notion, from the master's degree, of the importance of the pharmacovigilance system to the safety and control of marketed medicines it became stronger and sustained by experience of working at UFLVT. Most of the formation that I had during the master's degree on pharmacovigilance was theoretical principles and processes, the internship allowed me to apply those in real situations and to use SVIG which is a specific database used in the Portuguese pharmacovigilance system.

The most challenging moment in this internship was during my time at pharmacovigilance. When someone reported a couple ADRs from the same drug which involve life-threatening. One of them even developed to the patient's death, which later came to be declared as not related to the reaction. The reporter suspected of quality problem. While the medical coordinator of the UFLVT, Dr. Mário Miguel Rosa warned us to be aware because it could be related to a safety case. Once there's a suspicion of quality problem, there must be an intensive evaluation of the unit before sending a signal to the INFARMED. If it's actually confirmed the lot would have to be removed from market. In case it is a safety problem is more serious since the drug would have to be withdrawn from circulation. With the aggravating circumstance that this medication was the only available therapeutic for a specific groups of cardiac pathologies. Meaning that withdrawing this would imply the worsening or even death of patients with this pathology by lack of therapeutic alternative.

So under pressure and running against time me and Dra Ana Augusto, started scrutinizing the reports, the SPC of the medicine and asking for more information to the reporter in order to elaborate a kind of report. One thing that was strange since the beginning was that the medicine was already approved for about 10 years. It would be strange to discover such a serious safety problem, for a drug approved and used for so long in many different European countries. Some of them with more developed pharmacovigilance system than others.

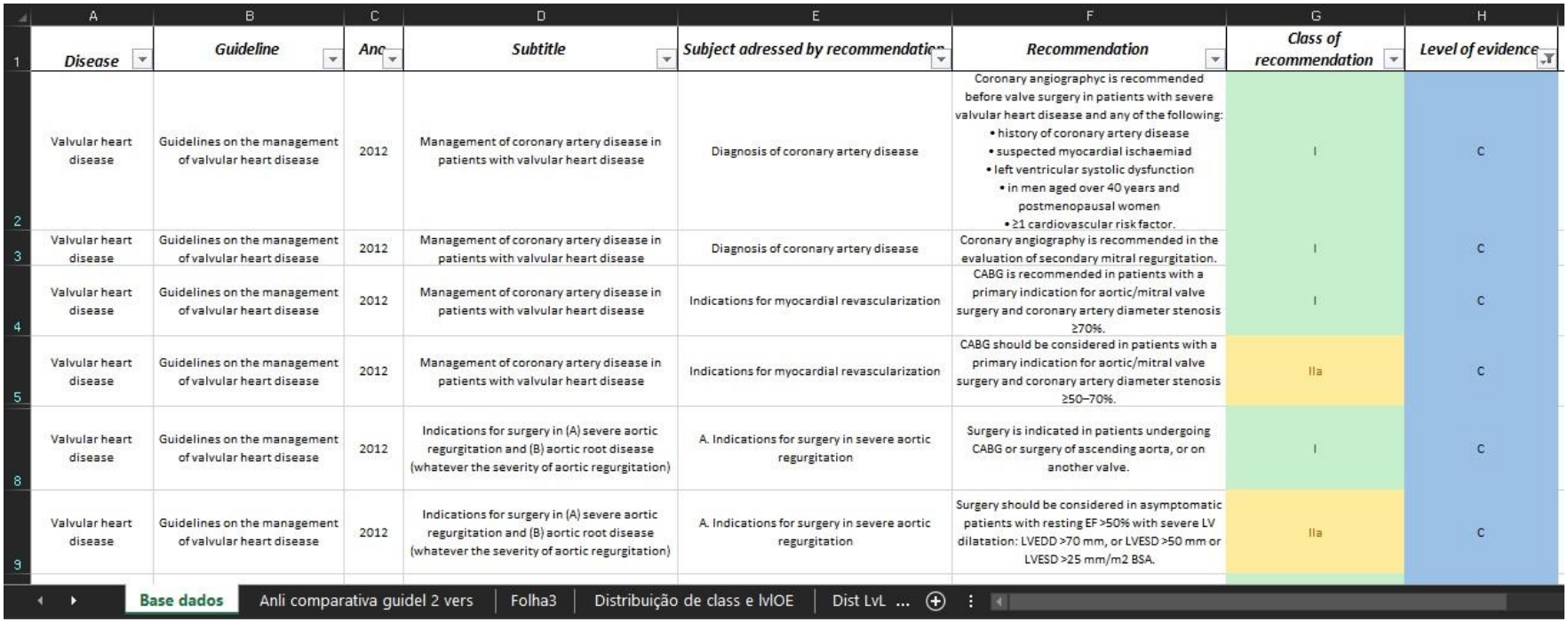
Some of the questions made to the reported where:

- What were the storage conditions of the drug?
- What was the preparation of the medicine?
- Since it was an injectable solution. What were the doses?
- How was the administration made? Ask for clarification about why the reporter considered a quality problem.
- There were visible changes in medicine, for instances strange colour, strange odour, deformities in the packaging?

After obtaining this additional information we compared it with the information from the medicine's SPC. And we come across the dose used by the institution was higher than what was present in the SPC thus we suspected overdose, later confirmed by Dr Mário Rosa and Dr Daniel Caldeira. We then elaborated a report with all the gathered information and our opinions and sent them to INFARMED who would have the last and final word on the subject. The action taken by INFARMED is not of our knowledge.

This episode made me build my capacity to work under pressure and against time. And also it allowed me to develop my judgment and critical spirit due to the fact that I had to analyse the RCM and look for flaws in the report and additional information of the ADR.

At my time working with systematic reviews and meta-analysis allowed me to work with databases and apply my statistical bases acquired during the master's and bachelor. For the systematic review of the ESC Clinical Practice Guidelines I had to build my own database with all the recommendations. After a draft and one or two trial and error, I came up with a solid database to work with (Figure 2). The database contained 4823 recommendations and their classifications which together amount a total 38584 entries on the database. This was all gathered by myself, and It was a job that required a lot of patience, persistence and attention. After finishing the database, I performed a descriptive statistical analysis and helped Dr. Daniel Caldeira writing the methods section of a paper. These activities allowed me to apply and develop the skills and knowledge about statistics and medical writing acquired in my formation. The meta-analysis on the influence of caffeine consumption in the risk of Cardiovascular Diseases (CVD) in patients with previous myocardial infarction was an opportunity to deepen my knowledge in the systematic review area, doing a scientific research, developing a formal protocol with RevMan. Working with RevMan was a new experience for me which I consider has being very advantageous, because It is one of the most used programs for meta-analysis (46). The guidance of Dr. Daniel during this time was essential since He is an expert in Systematic Reviews and meta-analysis. He contributed with all his knowledge was very kind and helpful because He showed me how It should be done and then let me work by myself. Helping when need. The working process was also a learning process.



	A	B	C	D	E	F	G	H
1	*Disease*	*Guideline*	*Anc*	*Subtitle*	*Subject adressed by recommendation*	*Recommendation*	*Class of recommendation*	*Level of evidence*
2	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Management of coronary artery disease in patients with valvular heart disease	Diagnosis of coronary artery disease	Coronary angiographyc is recommended before valve surgery in patients with severe valvular heart disease and any of the following: • history of coronary artery disease • suspected myocardial ischaemiad • left ventricular systolic dysfunction • in men aged over 40 years and postmenopausal women • ≥1 cardiovascular risk factor.	I	C
3	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Management of coronary artery disease in patients with valvular heart disease	Diagnosis of coronary artery disease	Coronary angiography is recommended in the evaluation of secondary mitral regurgitation.	I	C
4	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Management of coronary artery disease in patients with valvular heart disease	Indications for myocardial revascularization	CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥70%.	I	C
5	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Management of coronary artery disease in patients with valvular heart disease	Indications for myocardial revascularization	CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥50–70%.	IIa	C
8	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Indications for surgery in (A) severe aortic regurgitation and (B) aortic root disease (whatever the severity of aortic regurgitation)	A. Indications for surgery in severe aortic regurgitation	Surgery is indicated in patients undergoing CABG or surgery of ascending aorta, or on another valve.	I	C
9	Valvular heart disease	Guidelines on the management of valvular heart disease	2012	Indications for surgery in (A) severe aortic regurgitation and (B) aortic root disease (whatever the severity of aortic regurgitation)	A. Indications for surgery in severe aortic regurgitation	Surgery should be considered in asymptomatic patients with resting EF >50% with severe LV dilatation: LVEDD >70 mm, or LVESD >50 mm or LVESD >25 mm/m2 BSA.	IIa	C

Base dados | Anli comparativa guidel 2 vers | Folha3 | Distribuição de class e lvlOE | Dist LvL ...

Figure 2 - Print screen of the database build to the systematic review of ESC guidelines

Working as project manager/study monitor with Professor Ricardo Fernandes was of great responsibility. As study monitor of his observational study - *"Projeto ALFABETO: Alto Fluxo – Antever na Bronquiolite a Eficácia Terapêutica e Outcomes"* I should keep all the site documentation of the observational study updated. For this purpose, I raised any query, if applicable for every subject CRF that arrived from the participating centers. The queries aimed to point some information that was incomplete, not coherent, or against the protocol. And acted as a flag for everything that has to be corrected. This experience permitted me to apply the knowhow acquired during the master's but also permitted to mature some skills like attention to detail, organization and patience in order not to miss out on any mistake. Because letting something pass means introducing bias on the final analysis or lost data. It was also my responsibility to transfer the CRF data on paper to electronic CRF, and archive the same, create and change some of the source documents as the protocol or the Informed Consent, which involved a lot of medical writing. Once again this was a great opportunity to apply all the knowledge acquired in my formation.

In the preparation of ERS task force I had to establish contact with many international referenced paediatricians, introduce them to the Task force proposal and invite them to participate. It was a great way to expand my working network. From those who accepted I asked for their curriculum and declaration of conflict of interest duly completed. I merged all in a final document that was then revised by Professor Ricardo and sent as the official proposal to ERS.

Is important to note that during my internship I rotated through different services and the people I worked with also changed, this made me a flexible person and a better team worker.

The daily routine, and the responsibilities were very different of what I was used to at university. But I adapted well, and am a better human being and professional than I were before.

5. Conclusion

This internship was of great importance in my professional and personal development mainly because of its interdisciplinarity. Since this was my first professional experience in the clinical research environment it was good to face a variety of challenges and develop work in various areas of clinical research. Not only to apply the different knowledge acquired during my academic time but also very important to realize which path I want to take in my professional career.

Despite all the controversies, and stressful situations which are normal it was an experience that allowed me to grow professionally and humanely. Forced me to develop my sense of responsibility and allowed me to realize that in professional world not everything is done by the books, and not everything is taught. Some problems of everyday life must be resolved through the use of our capabilities, whether intellectual or humanistic character. I realized that if you are working for a greater cause and in favour of others which is example coordinating clinical trials It will keep you motivated and engaged to your work.

This internship was also a outstanding opportunity to expand my network and to work alongside some of the great names of Health in Portugal such as Dr. Mario Miguel Rosa and Professor Joaquim Ferreira.

It was a big challenge and for that I am proud of myself. I recognise that I'm still very inexperienced and for that reason I aspire for what is to come.

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