**EUNICE FERREIRA VICENTE**

# ESTÁGIO CURRICULAR NUM CENTRO DE INVESTIGAÇÃO CLÍNICA

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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 científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa, e da Professora Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada do Departamento de Ciências Médicas da Universidade de Aveiro.**

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**o júri**

| | |
|---|---|
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**palavras-chave**

investigação clínica, ensaios clínicos, farmacovigilância, monitorização, coordenação, centro de investigação clínica, *medical writing*, revisões sistemáticas.

**resumo**

O presente relatório de estágio descreve as atividades e projetos desenvolvidos no âmbito do estágio curricular numa unidade de farmacologia clínica (CPU), liderada pelo Professor Doutor Joaquim Ferreira, desde Setembro de 2015 até Junho de 2016. Este estágio foi realizado como parte do plano de estudos do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Neste relatório serão abordadas as atividades de coordenação de estudos clínicos, bem como as atividades o âmbito da formação em Farmacovigilância e *medical writing* que tive a oportunidade de desenvolver.

No decurso do estágio, tive a possibilidade de pôr em prática os conhecimentos adquiridos ao longo da minha formação académica e aprofundar o meu conhecimento sobre investigação clínica, numa perspetiva prática, bem como perceber as interações entre os diferentes profissionais. Tive ainda a oportunidade de compreender a realidade administrativa, logística e de gestão com que um centro de investigação se depara na condução de ensaios clínicos.

Por outro lado, tive também a possibilidade de experimentar diferentes papéis ligados à investigação clínica e compreender as responsabilidades e expectativas envolvidas em cada um deles. Para além disso, este estágio permitiu-me melhorar as minhas competências e perceber os meus interesses, capacidades, pontos fortes e fracos.

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

**keywords**

clinical research, clinical trials, pharmacovigilance, monitoring, coordination, clinical research center, medical writing, systematic reviews.

**abstract**

The present internship report describes the activities and projects developed under the curricular internship in a clinical pharmacology unit (CPU), led by Professor Joaquim Ferreira, from September 2015 to June 2016. This internship was carried out as part of the second year plan of the Master's Degree in Pharmaceutical Biomedicine of the University of Aveiro.

This report will address the activities I had the opportunity to conduct during the internship, focusing on my tasks as a trainee in clinical trial coordination, as well as activities related to Pharmacovigilance training and medical writing.

During the internship, I had the opportunity to put into practice the knowledge acquired throughout my academic training and deepen my knowledge of clinical research in a practical perspective. I was also able to perceive the interactions between different professionals working in clinical research. This internship also provided me with an opportunity to understand the administrative, logistics and management requirements that a research center faces during the conduction of clinical and observational trials.

Lastly, I also had the chance to train in several different roles linked to clinical research and grasp the responsibilities and demands that are required in each of them. Furthermore, this internship allowed me to improve my skills and understand my interests, capacities, strengths and weaknesses.

In conclusion, I can state that this internship was an enriching learning experience, both on a professional and personal level, with the main established objectives being achieved.

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# Abbreviations

| | |
|---|---|
| **ADR** | Adverse Drug Reaction |
| **AE** | Adverse Event |
| **CAML** | *Centro Académico de Medicina da Universidade de Lisboa* |
| **CEC** | Committee of Competent Ethics |
| **CEIC** | Portuguese Ethics Committee for Clinical Research (*Comissão de Ética para a Investigação Clínica*) |
| **CES** | Ethics Committee for Health |
| **CHLN** | North Lisbon Hospital Centre (*Centro Hospitalar de Lisboa Norte*) |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CNPD** | National Commission for Data Protection (*Comissão Nacional de Proteção de Dados*) |
| **CPU** | Clinical Pharmacology Unit |
| **CRF** | Case Report Form |
| **CRO** | Contract Research Organization |
| **CT** | Clinical Trial |
| **eCRF** | Electronic Case Report Form |
| **EEA** | European Economic Area |
| **EMA** | European Medicines Agency |
| **EU** | European Union |
| **FDA** | Food and Drug Administration |
| **FMUL** | Faculdade de Medicina da Universidade de Lisboa |
| **GCP** | Good Clinical Practices |
| **GLP** | Good Laboratory Practices |
| **HSM** | Hospital de Santa Maria |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IMM** | *Instituto de Medicina Molecular* |
| **INFARMED** | National Authority of Medicines and Health Products (*Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.*) |
| **IPQ** | *Instituto Português da Qualidade* |
| **IRB** | Institutional Review Boards |
| **ISF** | Investigator Site File |
| **IVRS** | Interactive Voice Response System |
| **IWRS** | Interactive Web Response System |
| **LCPT** | Laboratory of Clinical Pharmacology and Therapeutics |

| | |
|---|---|
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MS** | Multiple Sclerosis |
| **OS** | Observational Study |
| **PAES** | Post-Authorisation Efficacy Study |
| **PASS** | Post-Authorisation Safety Study |
| **PPMS** | Primary Progressive multiple sclerosis |
| **PRMS** | Progressive Relapsing Multiple Sclerosis |
| **PI** | Principal Investigator |
| **PL** | Package Leaflet |
| **PNEC** | *Plataforma Nacional de Ensaios Clínicos* |
| **QMS** | Quality Management System |
| **RCT** | Randomized Clinical Trials |
| **RNEC** | *Registo Nacional de Estudos Clínicos* |
| **RRMS** | Relapsing-Remitting Multiple Sclerosis |
| **SAE** | Serious Adverse Event |
| **SC** | Study Coordinator |
| **SNF** | National Pharmacovigilance System |
| **SOP** | Standard Operating Procedure |
| **SPC** | Summary of Product Characteristics |
| **SPMS** | Secondary Progressive Multiple Sclerosis |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **UFLVT** | Lisbon and Tagus Valley Regional Pharmacovigilance Unit (*Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo*) |
| **URF** | Regional Units of Pharmacovigilance |
| **WHO** | World Health Organization |

# 1. Introduction

The present document describes my curricular internship at the Clinical Pharmacology Unit (CPU) of the *Instituto de Medicina Molecular* (IMM), as part of the second year of the Master's Degree in Pharmaceutical Biomedicine of the University of Aveiro. This internship took place from September 14th 2015 to June 28th 2016.

As stated earlier, this internship was held at the CPU, which is a research unit of IMM. IMM itself is a part of the *Centro Académico de Medicina de Lisboa* (CAML). The CAML is a conglomerate formed by three entities: *Centro Hospitalar de Lisboa Norte* (CHLN) – Hospital de Santa Maria (HSM), the *Faculdade de Medicina da Universidade de Lisboa* (FMUL), which is an integrated institution of higher education at the University of Lisbon, and the aforementioned IMM (1,2). During the internship and due to the characteristics of the host institution, I had the chance to work in several departments and different areas dealing with research and development of new drugs.

At first, I had an active role as a project manager trainee for an observational study (OS), alongside data management tasks; afterwards, I collaborated in pharmacovigilance activities at the *Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo* (UFLVT). After that, I worked as a clinical trial coordinator trainee, and had the opportunity to be actively involved in clinical trial coordination activities such as data management, study coordination, and sample processing. At the end of the internship, I returned to medical writing and data management activities. All these assignments performed during the nine months of training were done under supervision of Professor Joaquim Ferreira, the group leader of CPU.

The aim of this internship was to strengthen and improve my knowledge about clinical research, including clinical trials (CT), medical writing and pharmacovigilance. I also wanted to gain skills in a real workspace environment.

The expected learning objectives for this on-the-job experience on the CPU were defined at the beginning of the internship, and have been updated to better reflect the different challenges and activities that occurred during its course. The final learning outcomes defined for this internship are described below:

- Understand the inner workings of a clinical research unit;
- Develop skills on all procedures and steps related to CTs;
- Know and, if possible, gain experience on the regulatory process guiding CTs;
- Acquire knowledge about the activities of a regional pharmacovigilance unit;
- Obtain awareness on the reality of pharmaceutical research;
- Improve my writing skills;

- Improve my personal and soft skills, such as teamwork, critical thinking, problem solving, organization, communication, autonomy, intuition and self-confidence;
- Write a scientific paper related to clinical research.

This report is structured in chapters and subchapters, beginning with an introduction and the objectives of my curricular internship.

In the second chapter an overview of the host institution is provided, with a brief description of their objectives and activities.

The third chapter provides a discussion on the state of the art of clinical research, including its conception, evolution, the development and the conduction of CTs. The current state of Portugal in the conduction of CTs is also discussed. Two other themes are also reviewed, including pharmacovigilance and the National Pharmacovigilance System, and finally medical writing.

In section four the developed activities are described in detail, by chronologic and department order.

This report ends with a global conclusion on the curricular internship, including the main obstacles faced, also the professional and personal skills improved during this period.

# 2. Vision of the Host Institution

In the following chapter it will be described the Host Institution's work unit, their objectives and activities.

## 2.1. Institute of Molecular Medicine (*Instituto De Medicina Molecular*)

IMM is located on the campus of the FMUL, and it is an associated laboratory to the National Ministry of Science and Higher Education (3). The laboratory was funded in December 2002, and IMM was the result of an association that joined five former research units existing in the FMUL: the Biology and Molecular Pathology Centre, the Microcirculation and Vascular Pathobiology Centre, the Lisbon Neurosciences Centre, the Gastroenterology Centre and the Nutrition and Metabolism Centre (3). The Institute is a private, non-profit association, and is mainly supported by national and European Union (EU) funds, alongside research grants, private donations and industrial partnerships (3).

The Institute's mission is to foster basic, clinical and translational biomedical research, with the goal of contributing to a better understanding of disease mechanisms. These include the development of novel predictive tests, improving diagnostics tools and fostering new therapeutic approaches (3).

### 2.1.1. Clinical Pharmacology Unit

The CPU, also known as Joaquim Ferreira Lab, is one of IMM's research laboratories, and was formally created on July 1, 2013, with members of the research team of the Neuropharmacology Unit of the Neurological Clinical Research Unit alongside the Laboratory of Clinical Pharmacology (Faculty of Medicine) (3,4).

The CPU is located at the Laboratory of Clinical Pharmacology and Therapeutics (LCPT), on the third floor of HSM. Its core mission is to contribute to the development of effective and safe therapeutic interventions by setting up optimized methodologies for the design, conduction, analysis and report of CTs (3,4). The main work areas of the CPU include CT methodology, CTs outcomes, systematic reviews, drug safety, magnetic resonance imaging and drug use (3).

The internship was leaded under the supervision of Professor Joaquim Ferreira, the director of the CPU. Joaquim Ferreira is a neurologist, who is a university professor and researcher. His core areas of interest are movement disorders, neuropharmacology, Parkinson's disease, muscle dystonias, botulinum toxin and Huntington's disease.

#### 2.1.1.1. Clinical Trials Sub-Unit

The Clinical Trials Sub-Unit is located on the sixth floor of the Neurology Department of the HSM. Its main activities include the conducting of CTs, mostly for new therapies for neurological disorders. Since its founding in 1999, more than a hundred of studies have been performed there. As stated above, this unit is focused on CTs on neurological conditions, such as multiple sclerosis, familial amyloid polyneuropathy, Parkinson's disease, Alzheimer's disease, epilepsy and psychosis.

The centre is mainly run by two study coordinators (SC), Dra. Ana Noronha, who has more than fifteen years of experience in CTs, and Dra. Ana Salgueiro, who has a Master's Degree in Pharmaceutical Medicine and two years of experience in clinical trial coordination. The team is composed of many more professionals, including physicians specialized in various diseases being studied here, nurses, psychologists and neuro psychologists.

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

This sub-unit integrates the Movement Disorders Cochrane Collaboration Review Group. The Cochrane Movement Disorders Group was created in 1996 and is located at the CPU. This group is affiliated with the Cochrane, which is an international non-profit organization, composed of researchers, health professionals and patients (5).

The Cochrane group works in collaboration with professionals all over the world to create Cochrane Reviews, providing systematic reviews of the benefits and risks of healthcare interventions (5,6). A systematic review is a scientific paper that collects and critically analyzes multiple research studies.

As the group name reveals, the Cochrane Movement Disorders Group provides systematic reviews of movement disorders, a subspecialty of Neurology which includes conditions such as idiopathic Parkinson's disease, Huntington's disease, dystonia, tremor and multiple system atrophy. The movement also has reviews covering other topics like depression, dementia and pain in movement disorders patients (6).

#### 2.1.1.3. Biostatistics and Methodological Sub-Unit

The Biostatistics and Methodological Sub-Unit was created by necessity, in order to support the activities developed by the unit itself. It provides support in statistics, medical writing, and also project and clinical data management to all research projects. This support can cover a broad area, such as study design optimization, analysis and report of clinical research, and methodical support on systematic reviews.

#### 2.1.1.4. Safety and Drug Utilization Research Sub-Unit

This sub-unit, also known as UFLVT, is a part of the CPU since 2013, and it is one of the regional units of the Pharmacovigilance National System (SNF). Created in 2003, following the decentralization of the Pharmacovigilance System in 1999, the UFLVT has been charged by the National Authority of Medicines and Health Products (INFARMED) to perform pharmacovigilance duties in connection with the SNF (7). The UFLVT main activities include: to receive, classify, process, validate and attribute causality of the spontaneous notifications of adverse events (AE); to promote the safe and rational utilization of medicines; to promote pharmacovigilance actions by organizing related training; to collaborate with the INFARMED in the SNF; and to propose and develop pharmacoepidemiologic studies, surveys, and scientific publications.

The unit has four permanent people working: Dr. Mário Miguel Rosa, the director of the pharmacovigilance unit and clinical assessor, responsible for the attribution of the causality to the adverse drug reactions (ADR); Dr. Ana Marta Anes, who is the principal responsible for pharmacovigilance tasks concerning ADRs processing, generation of warning signs and pharmacovigilance training/awareness duties; Dr. Ana Augusto, a pharmacovigilance technician, and the one responsible for quality assurance, guaranteeing that processes needed for the Quality Management System (QMS) are established, implemented and maintained; and Carolina Gaspar, the administrative assistant, responsible for database management of the UFLVT and secretarial work Finaly, Ema Roque who is the person responsible for the financial and administrative management of resources in the UFLVT.

#### 2.1.1.5. Outcomes Sub-Unit

The outcomes sub-unit was created in order to study the design and validation of outcomes in CTs. This sub-unit focus its efforts on the evaluation of rating instruments used in CTs and validation of CT outcomes, issuing systematic reviews and meta-analysis, mainly in areas such as bronchiolitis, recurrent wheezing and asthma as well as in biomarkers and patient reported outcomes from drug evaluation.

# 3. State of the Art of Clinical Research

The aim of this section is to provide an overview about the main areas related to the on-the-job training, such as the main procedures to create, authorize and conduct a CT, the current state of Portugal in the conduction of CTs, pharmacovigilance and medical writing.

## 3.1. Clinical Research

Clinical research is any research that directly involves a particular human being or group of people, or that uses materials from humans, such as samples of their tissues, specimens and cognitive phenomena (8). With it, we can learn how to prevent, diagnose and treat diseases that concern to the population. Clinical research is a term that serves as an umbrella for many others in scientific investigation: it can go from basic research to new treatments and innovation that can benefit patients.

## 3.2. Evolution of Clinical Research

### 3.2.1. Evolution of Ethical and Regulatory Framework

The first steps for the establishment of the ethical framework for human subject protection was taken with the Hippocratic Oath, where it's specified a prime duty of a physician – to avoid harming the patient. Throughout history, however, this oath was not respected multiple times (9). Many human abuses were committed, mostly during World War II, an these unfortunate events have create the need to develop drug regulation more than the evolution of a knowledge base (9,10).

The first planned and controlled CT happened in 1747, when James Lind planned a comparative trial, in order to find the most promising cure for scurvy, due to the high mortality amongst sailors in the ship in which he was working at the time as a surgeon (9). Even though James Lind did not have access to the guidelines and laws we now have, the trial he made contained the basic elements of a CT: he tried to have twelve similar patients and put them all on the same diet (9). Then, he divided the twelve scorbutic sailors into six groups of two and selected six of the most promising treatments (9,11). With this CT, it was undoubtedly made clear that the treatment with best visible results to cure scurvy was acid fruits (9).

Since the late nineteenth century, numerous attempts to regulate scientific activities have emerged. On March 2, 1900, US Senator Jacob H. Gallinger proposed to the US Senate a law regulating scientific experiments on human beings (12). The research, according to this proposal, could only be performed by qualified professionals, and that babies, children, adolescents, pregnant women, nursing mothers, old and mentally ill would not be eligible for research. Moreover, research subjects should have over twenty years old and be in full capacity to make decisions, since no experiment should be conducted against the will of its participants (12). Although this proposal has

not been accepted, it was the first document that established clear rules for conducting research in humans (12).

Also in 1900 the Prussian government issued regulations on human experimentation – The Berlin Code - and these directives were the first modern regulations by a state authority (13). The concepts of these directives were similar to the law proposed by Jacob Gallinger, such as the fact that research on children and noncompetent persons would not be allowed in any circumstances (13).

Afterwards, in 1931 in Germany, guidelines were established for therapeutic and scientific research on human subjects, which are thought to be the first of their kind (14). It is interesting to note the disjunction between these guidelines and the practice of the Nazi researchers during World War II, where the ethics of human experimentation were left behind and the respect for the human being was lost, and many atrocities have been committed, first and foremost against the Jewish people.

One of the consequences of the Trials of War Criminals before the Nuremberg Military Tribunals occurring at the end of World War II, where a series of trials were held for war crimes against survivors head members of Nazi Germany who were accused of conducting torturous human experiments at the concentration camps, was the Nuremberg Code, issued in 1947 (15). The Nuremberg Code is a set of ethical principles governing research with human beings. It has ten basic principles, mainly based on the guidelines established on 1931, establishing the standards of informed consent and absence of coercion, regulating scientific experimentation and defending beneficence as one of justifiable factors to the participants on the experiments (15,16). The Nuremberg Code has no legal force behind it, but its influence on global human-rights law and medical ethics is quite profound.

Just one year later, in December of 1948, it was adopted by the United Nations the Universal Declaration of Human Rights (17). It is an international document that states basic rights and fundamental freedoms to which all human beings are entitled, and it's undoubtedly a reflection on the previous barbaric events. The Universal Declaration starts by recognising that '*the inherent dignity of all members of the human family is the foundation of freedom, justice and peace in the world*'; furthermore, it declares that human rights are universal, and should be achieved by all the people, no matter who they are or where they live (17). It includes civil and political rights, such as the right to life, privacy, liberty and free speech; and also comprises economic, social and cultural rights, like the right to social security, health and education (17).

Despite the progress these guidelines have had on human rights, the development of medicines regulation was still precarious, particularly when it came to safety studies. Two catastrophes have catalysed this development.

In 1937 a sulfanilamide elixir, a drug used to treat streptococcal infections, killed over 100 people in the United States (10). The company which sold the elixir did a series of tests, establishing that sulfanilamide would dissolve in diethylene glycol, and tests for mixture for appearance, flavour, and fragrance. However the most important test was outright ignored: how the drug would react in the human body – toxicity testing (18,19). By this time, it was not neither illegal nor required for new drugs to undergo through safety studies.

This catastrophe facilitated the introduction of The Federal Food, Drug and Cosmetic Act in 1938, with the premarket notification requirement for new drugs and preclinical tests of toxicity (10,18,20). This gave the United States a new system of drug control, that provided protection to the population, while stimulating medical research and progress; this same system would prevent a bigger tragedy twenty three years later, the thalidomide disaster (10,18).

The thalidomide disaster influenced the development of medicines regulation far more than any event in history. Thalidomide was a widely used over-the-counter drug that appeared in the late fifties, for the treatment of nausea in pregnant women (21). But when multiple statements reported birth defects as phocomelia, neonatal deaths and miscarriages in children exposed to the drug during the gestation in fifty countries approximately (mostly in Europe, the drug did not reach commercialization in the USA), between 1958 and 1962, it become apparent that pharmaceutical products should be systematically tested for developmental effects prior to marketing, in order to prevent such abominable AEs and safeguard public health (10,21).

As a result, the whole regulatory system was reshaped in Europe, and stricter medicines regulations were established in order to protect public health and also to prevent a fledgling single market turning into a fragmented one, which would debilitate the competiveness of the European pharmaceuticals industry (22). In 1965 the EU Council approved the primal legislation on pharmaceutics of the EU, defining what a “medicinal product” was. It is since then required that a drug must be approved for marketing only when proving the evidence of the quality, safety and efficacy, as well as respecting basic rules on testing requirements (22,23).

Although the US Federal Pure Food and Drugs Act -1906, and the Federal Food, Drug and Cosmetic Act – 1938 were already in place when the thalidomide tragedy occurred, a subsequent New Drug Amendment – the Kefauver-Harris Amendment in 1962 appeared, stating that both a proof of efficacy and safety is mandatory before commercialization of a drug product. FDA started to monitor all stages of drug development – furthermore, investigational drugs required comprehensive animal testing before moving to human CTs (22).

It is worth noting that the World Medical Association considered that the Nuremberg Code had some flaws, and efforts were made to update it at the 18th World Medical Assembly (1964) in Helsinki, Finland (24). This document - the Declaration of Helsinki, developed the first ten principles

espoused in the Nuremberg Code, and allied to the Declaration of Geneva (1948), a statement of ethical duties of the physician (24,25). Mostly directed to clinical research, the Declaration of Helsinki requested changes in medical practice from the concept of human experimentation used in Nuremberg Code, being one the flexibility of the conditions of authorization, which was absolutely essential in the Nuremberg Code (24,25). Doctors were asked to obtain consent if at all possible, and the possibility of investigation was authorized with proxy consent, when a legal guardian was available (24,25). This document has become a benchmark in most national and international guidelines, advocating in the first place the statement that the welfare of the human being should take precedence over the interests of science and society (24).

Even though the notions of ethics have improved and there were then rules and directives to follow regarding this matter, highly unethical human experiments continued to occur. An example of such experiments was the Jewish Chronic Disease Hospital Case, in 1963, where three doctors injected live cancer cells in patients chronically ill in order to study the rate of rejection in patients already afflicted by some diseases. Patients were not informed the cancer cells would be injected nor they were they told about they were the subjects of an experiment, which is a serious violation of fundamental human ethics (26). Another example was the Willowbrook Case, from 1956 to 1972, when mentally handicapped children housed at the Willowbrook State School were intentionally given hepatitis in an attempt to track the development of the viral infection (27). This study failed to comply with several ethical points, first being that the research was not done for the benefit of the children involved, and second because a deliberate infection of a person with an infectious agent as a part of any research is unacceptable. Moreover the parents who consented, other than being unaware of the risks, were coerced into enrolling their children in the research due to the lack of available space at the school (27,28). One last example, maybe the most shocking, was the Tuskegee Syphilis Study conducted by the U.S. Public Health Service, in which 400 men with syphilis where used as test subjects and 200 uninfected men who served as controls, to determine the prevalence of syphilis among blacks and observe the evolution of disease when free of treatment (29). At that time, it was plausible to do that, because a treatment for syphilis was not available. However, the subjects were never told they had the disease, but simply that they had bad blood and they would receive a free treatment (29). Penicillin appeared in the 50s, but these patients never ended up receiving it, which is denial of the best available treatment to a patient. Nevertheless, the investigators decided to continue the study and even prevented some men from seeing physicians who could help them (29,30). As a result, countless people died a painful death, many became permanently blind or insane, and some children of them were born with congenital syphilis (29,30).

These cases and many others have been reported in the book 'Human Guinea Pigs: Experimentation on Man' by Maurice Henry Pappworth, a British medical ethicist who intended to expose the unethical dimensions of medical research (31,32).

As expected, the regulations have tightened and the Helsinki Declaration was revised at 1975, aimed to increase the protection of the research subject while not inhibiting medical research unnecessarily (25). This new revision clearly stated that "concern for the interests of the subject must always prevail over the interests of science and society". It also has added the requirement for independent committees to review research protocols, and thus created the necessity of research ethics committees or ethical review boards in Europe and a system of Institutional Review Boards (IRB) in the US (25).

Yet the change in good practices in clinical research did not end here. The concept of 'Good Clinical Practice' was first defined in the USA as a result of concerns about the authenticity and quality of some research data submitted to the regulatory authorities for drug authorization to market (33,34). In an attempt to ensure data quality and protect the research subjects, FDA published the first guidelines for clinical research, that was followed by other countries (34).

In 1978, the four principles of respect for autonomy, non-maleficence, beneficence, and justice on clinical research were introduced in the 'Principles of Biomedical Ethics' by Beauchamp and Childress (35). The introduction of these principles has brought a new vision on the need to give the patients the right to self-govern, in order to protect his or her autonomy: do no harm; maximize benefits and minimize risks, in order to beneficence all patients; and select the participants equitably and avoid exploitation of vulnerable populations, so the sense of justice would be equal to everyone (35).

These principles are also referred in the Belmont Report, by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, in 1979 (36). The Belmont Report also defined a method that IRB members can use to determine if the risks to those being subjected to research are justified regarding the benefits to be gained. The purpose in this report was to make the assessment process more rigorous, reshaping the communication between the IRB and the investigator to be less ambiguous, and more factual and precise (36).

Furthermore, in 1982 the Council for International Organizations of Medical Sciences (CIOMS) published the International Ethical Guidelines for Biomedical Research Involving Human Subjects (37). Actually, these 21 Guidelines (15 in the original report) address issues including informed consent, standards for external review, recruitment of participants, and more. The Guidelines are general instructions and principles of ethical biomedical research (37).

In 1996 the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) introduced the Guideline for Good Clinical

Practices (GCP), which served as the basis for harmonization for CTs to be conducted in different locations such the US, Europe and Japan, in harmony with high ethical and scientific standards (38).

In 1997, Portugal and other 20 European countries signed in Oviedo an international document – the Convention for the Protection of Human Rights and Dignity of the Human Being - with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, in order to protect the dignity and identity of all human beings and to guarantee to all persons, without discrimination, respect for their integrity and the other rights or fundamental freedoms related to the application of biology and medicine (39,40). The Convention is the first legally-binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances. It lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation, public debate, etc. (39)

Moreover, the latest amendment to the Declaration of Helsinki (2013) highlights the need to disseminate research results, including negative and inconclusive studies and also includes a requirement for treatment and compensation for damages to the patient related to the investigation (25). In addition, the updated version is considered more relevant for resource limited settings, since it address the need to ensure access to an intervention, if proven to be effective (25).

## 3.3. Observational Studies

An OS, also called natural experiment or *quasi* experiment, is an empiric investigation that tries to elucidate cause-and-effect relationships when randomized experimentation is unethical, unnecessary, inappropriate or infeasible (41). In other words, in an OS, the investigator can control treatment assignments and must seek a clear comparison in other ways (42). It is the result of an active search for those rare situations in which substantial evidence may be obtained to differentiate treatment effects from the most plausible biases, and involves the direct observation of people in their natural setting, when the only intervention that occur is data gathering (42,43). This data can be either collected by the investigator for the purpose of the study-primary data, or it has already been collected for another purpose but it is used by the investigator to examine a novel research question (secondary data), like data from patients clinic history collected by hospitals (43).

There are three main types of OS designs, presented in the table below:

**Table 1. Comparison of observational study designs (Adapted from Carlson et al.** (43)**)**

| | Brief description | Primary use | Disadvantages | Frequent Measures |
|---|---|---|---|---|
| *Cross-sectional* | Exposure and outcome are determined simultaneously for each subject | Screening hypotheses; prevalence studies | No evidence of a temporal relationship between exposure and outcome | Prevalence rates |
| *Cohort* | Subjects are followed over time, with individuals who are exposed and not exposed to a factor and then evaluate the subsequent development of an outcome | Assessing association between multiple exposures and outcomes over time | Losses to follow-up, alternative explanations for study results due to confounding, potential bias in outcome assessment | Relative risk |
| *Case-control* | Some individuals have the outcome ("cases") and are compared to individuals who don't have the outcome ("controls") according to past history of exposure to a factor | Assessing associations between exposures and rare outcomes | Interviewer bias | Odds ratio |

## 3.4. Clinical Trials

A CT can be defined as any investigation in humans being intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal product, or to identify any adverse reactions to one or more investigational medicinal product, or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product in order to determine the respective safety or efficacy (44–46). What primarily differentiates a CT of an OS in fact is that in CTs there is a change in the routine of the participants, and this change is evaluated in terms of health, to see if the results are positive, negative or they remain the same. It follows the participant from a well-defined point in time, which means it is a prospective study (45). To a CT occur, we need three things: an experimental unit, a treatment and the evaluation of it (44).

An experimental unit is what we call a subject from a targeted population under study. We need it because it's necessary to represent the intended study population from which the results of the study are inferenced (44). This experimental unit can be healthy subjects or patients with certain diseases, depending on which phase the CT is (44,45).

In CTs, a treatment is anything that can bring to the experimental unit any gains in health: a placebo, any combination of an investigational medicinal product, a surgical procedure, a diagnostic test, a medical device, a new diet, a health education program or even no treatment (44,46).

The goal of a CT is to evaluate the efficacy or safety of the intervention being tested. The evaluation can be trough laboratory parameters, questionnaires to health professionals, changes in the findings of physical examination, ADRs, pharmacogenomics, assessment of quality of life and even pharmacoeconomic criteria such as cost-minimization, cost-effectiveness and cost-benefit analyses associated with the treatment under study (44,45).

Randomization is the process by which the allocation of subjects to treatment groups is done by chance, without the ability to predict who is in which group (45,47). A randomized clinical trial (RCT) is a CT in which participants are randomly assigned to separate groups that compare different treatments, having an equal chance of receiving any of the treatments under study (47,48). They are considered the gold standard of study designs because the potential for bias - selection into treatment group - is avoided and prevents predictability, balances the groups in known and unknown confounding or prognostic variables - insures against accidental bias, and assures statistical tests (e.g., t-test, chi-square) will have valid significance level (48). Overall, a randomized experiment is an essential tool for testing the efficacy of a treatment.

Blinding or masking is a process used to increase the objectivity of the individuals like study participants, caregivers, investigators and staff who have contact with them, persons making laboratory measurements, data analysts, and those adjudicating outcomes dealing, when they have no knowledge of the study group assignment (8,45). In CTs, blinding is as important as randomization, in order to avoid potential problems of bias during data collection and assessment (8,45).

To achieve blinding, it is often used a placebo, that can be a medical treatment like a pill, a chemical solution or an operation which is administered as if it were a therapy, but having no therapeutic value other than the placebo effect. The placebo should appear identical in weight, taste, color, and odor to the drug in test (45).

### 3.4.1. Tasks and steps to setting up a clinical trial

In order to understand the phases of a CT, we firstly need to understand what happen prior to them. To obtain the approval to introducing a drug in market, a drug manufacturer must submit

the information about nonclinical (animal) and clinical (human) test data and analyses, the drug brochure, and the manufacturing procedures description.

#### 3.4.1.1. Pharmaceutical Research & Development

In an early phase of development, researchers try to identify an investigational drug and perform initial tests in the lab; this first stage of the process takes approximately three to six years (49). At the end, researchers expect to identify a promising drug candidate to further study in the laboratory and in animal models - pre-clinic studies, and then in people – CTs (49,50). During this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment; nevertheless, only a small number of compounds can surpass the early testing's and appearing as promising and eligible for further study (49,50). As a result, the average cost to research and develop a successful drug is estimated to be €2.3 billion, greatly due to thousands and sometimes millions of compounds necessary to be screened and assessed early in the R&D process that fail (49,50). The overall probability of a medicinal product to reach the CTs phase, and eventually be approved, is estimated to be around 8% (49,50).

#### 3.4.1.2. Pre-clinical studies

Before testing a medicinal product in the population, researchers must find out whether it has the potential to cause serious harm – safety studies. This includes pharmacodynamics - what the drug does to the body; pharmacokinetics - what the body does to the drug; absorption distribution, metabolism, and excretion; and toxicology testing (51). These nonclinical studies provide detailed information on dosing and toxicity levels of the drug; the main goals of this are to determine the safe dose for First-In-Man study and start to assess product's safety profile (51,52).

These kind of studies can be divided in two types: *in vitro* and *in vivo* (51,52). In vitro studies usually are performed with cell culture of human tissue, like liver or DNA (51,52). *In vivo* studies are conducted with animals, normally in two species, one rodent, one non-rodent: typically mice and dogs are chosen, although primates and pigs are also used (51,52).

To perform these preclinical studies, it is required the researchers to follow Good Laboratory Practices (GLP), as defined in medical product development regulations (51,52). After preclinical testing, researchers should review their findings and then decide whether the drug should be then tested out in people (51,52).

### 3.4.1.3. Phases of Clinical Development

Classically, trials of pharmaceutical products are divided in four phases (Phase I-IV). However, this classification seems to be an inadequate in the current landscape of clinical because one type of trial may occur in several phases, and chronological phases do not imply a fixed order of studies, as we can see in figure 1 (53). So, a classification system using study objectives appears to be better (53).

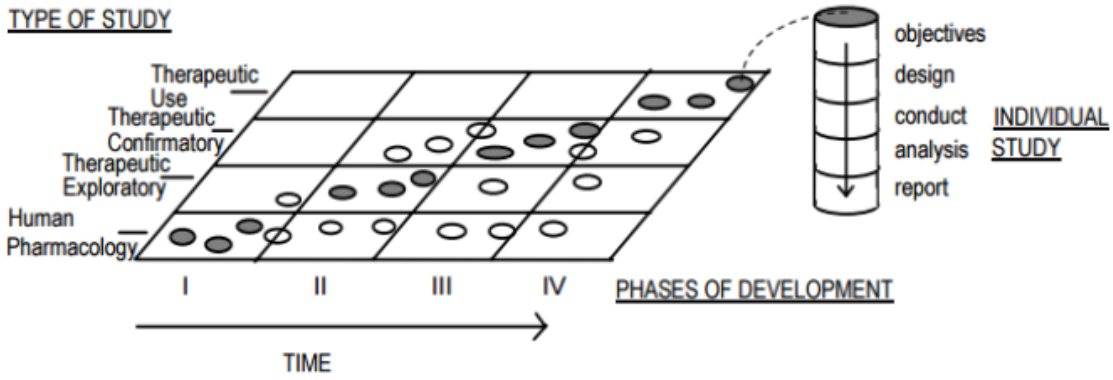


**Figure 1. Correlation between development phases and type of study. The shaded circles show the types of study most commonly conducted in a certain phase of development, and the open circles show certain types of study that may be conducted in that phase of development, but are less usual (Taken from '*E8 General Considerations for Clinical Trials*' (53))**

#### *3.4.1.3.1. Phase I*

Phase 1 trials are typically called First-in-human because they include the initial introduction of an investigational new drug into humans (52). The most typical types of study that occur during this phase are human pharmacology, and are designed to determine the metabolic and pharmacologic actions of the drug in humans, to estimate the side effects associated with increasing doses, and to gain early evidence on effectiveness and preliminary assessment of drug activity if possible. These trials also study bioavailability and body compartment distribution (45,53).

Studies in this phase of development usually extend for several months, having non-therapeutic objectives. These studies are usually conducted in healthy volunteer subjects. However, when the drug in test has significant potential toxicity, e.g. cytotoxic drugs, these studies should be conducted in patients (45,53).

During this phase, the sufficient information about the drug's pharmacokinetics and pharmacological effects must be gained in order to design well-controlled and scientifically valid Phase II studies (45,52,53). According to FDA, the percentage of drugs that moves to the next Phase is 70% (54).

#### *3.4.1.3.2. Phase II*

Once a dose or range of doses is determined, the next target is to evaluate whether the drug has any biological activity or effect – Therapeutic Exploratory trials (45). The following trials are usually randomised and concurrently controlled, aiming to evaluate the efficacy of the drug, find out an optimal dose strength, and studying the possible short-term side effects (AEs) and risks associated with the drug for a particular therapeutic indication (45,49).

This studies may use a variety of study designs, and the comparison may consist of a concurrent control group, like an inactive substance (placebo), historical controls, a different drug that is usually the standard of care for the disease or pretreatment status versus post treatment status (45,49,53).

Because of the uncertainty with regard to dose–response, phase II studies may also employ several doses, multiple intervention arms, and the patients are selected by relatively narrow criteria, creating an homogeneous population which one can be closely monitored (45,53). In this phase, the candidate drug's effectiveness is evaluated in 100 to 500 patient volunteers with the disease or condition under study, and it can extend up to two years (49,54).

This phase is usually divided in two: phase IIa and phase IIb. Phase IIa is usually an exploratory (non-pivotal) study seeks to study clinical efficacy, having pharmacodynamics or biological activity as primary endpoint (55). In this phase, the study can be conducted in patients or healthy volunteers (55). Phase IIb will usually assess one or two doses chosen from Phase IIa in patients with efficacy as primary endpoint (55). Exceptionally, Phase II studies can be used as pivotal trials if the drug is intended to treat life-threatening or severely-debilitating illnesses as in oncology indications (55).

If the drug continues to show promise, it can advance to larger Phase III trials. The percentage of drugs that goes to the next phase decreases drastically comparing to Phase I, reaching about 30% (54).

#### *3.4.1.3.3. Phase III*

This studies are often called therapeutic confirmatory studies, because they are generally designed to assess the effectiveness of the new intervention and thereby, its value in clinical practice (52,53). They are performed after a preliminary evidence evaluation of the drug, suggesting preliminary effectiveness of the drug, and are designed to generate statistically significant data about effectiveness and safety that is required to provide an adequate basis for assessing the overall benefit-risk relationship of the drug to support marketing approval (52,53).

Phase III studies also provide an adequate basis to extrapolate the results to the population in general and to transmit that information on the physician labelling information, such as the potential interactions with other medicines and specific dosing instructions (49,53). These studies usually include several hundred to several thousand people with less tight inclusion criteria; the drug is tested

in different stages of disease, or in combination with another drug; and the trials are larger and simple than those performed in the early stages (53).

Phase III trials are both the longest and costliest trials, often including hundreds of study sites at hospitals and centers both across the Europe and around the world (49,53).

#### *3.4.1.3.4. Phase IV*

Research on a new drug does not end when the discovery and development phases are completed and the medicine is available in the market (49,52). On the contrary, companies must conduct wide post-approval investigation to monitor safety, long-term side effects and identify less common ADRs, and improve their understanding of the benefit/risk relationship in general or special populations and/or environments (49,52).

Phase IV studies can be any kind of study performed after drug approval and related to the approved indication, rather than routine surveillance (49,53). These studies were not considered essential for licensing but they are commonly significant for optimising the drug's use (49,53).

This studies can include research in additional drug-drug interaction, safety studies or dose-response and also studies designed to support use under the approved indication, like pharmacoeconomic studies, epidemiological studies and studies on mortality/morbidity outcomes (49,52).

Two of the most commons studies carried out during this phase is the post-authorisation safety studies (PASS), in order to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures, and post-authorisation efficacy studies (PAES), in order to complement available efficacy data and assess the benefit risk balance of the medicinal product (56,57). This studies can be either be CTs or non-interventional studies (56). They can be also imposed when required by a competent authority, such as studies that are a specific obligation for a marketing authorisation granted under exceptional circumstances or other studies that a competent authority requests the company carry out, or voluntary, which include non-imposed studies that are requested in risk-management plans of the company (56).

### 3.4.2. **Legal and Ethic Approval of a Clinical Trial**

To be conducted in a European country like Portugal, either in a hospital or clinic, a CT must be approved by various authorities.

#### 3.4.2.1. INFARMED

According to the guidelines published by the European Commission, and under Portuguese legislation, each country should require authorization to the national Competent Authority to carry out a CT, a clinical study with the use of medical devices or cosmetics and body hygiene (58). For clarity sake, the Portuguese National Competent Authority is the INFARMED.

The request for an authorization to conduct CTs is submitted to the INFARMED, by the sponsor through the *Registo Nacional de Estudos Clínicos* (RNEC), and must be accompanied by various elements, such as the protocol, the investigator's brochure, the full name and qualifications of all stakeholders and the dossier of the investigational product (46). Within 30 working days, the governing board of the INFARMED will act on the request for authorization (46).

The European Medicines Agency (EMA) does not have an active part in the authorization of CTs, who take place in Member State countries, but plays a key role in safeguarding that the standards of GCPs are applied and fulfilled in the European Economic Area (EEA), with cooperation with the Member States (59). It also manages a database of CTs carried out in the European Union, which is available for consultation by everyone (59).

Moreover, inside the EMA, the Agency's Committee for Medicinal Products for Human Use (CHMP) is responsible for conducting the assessment for a medicinal product when a centralized marketing authorization in the EU is requested; as part of the scientific assessment, the CHMP needs to assess the CTs data included in the application (59).

#### 3.4.2.2. CEIC

The Portuguese Ethics Committee for Clinical Research (CEIC) is the committee in charge of issuing ethical evaluations on the establishment and approval of CTs in order to ensure the protection of the rights, safety and well-being of participants (46).

To be able to give their opinion on the CT, CEIC must assess the relevance and design of the protocol or research plan, the proposed intervention benefit-risk profile, the ability of the research team, human and material resources available in the research sites, the compensation for damages, insurance, amounts and the arrangements for rewarding researchers and participants, methods of recruitment, the way is guaranteed the autonomy of volunteers - particularly with regard to the nature and adequacy of information to be provided and the procedure for obtaining informed consent - and also the circuit and accessibility of the experimental drug (60). To give their opinion, CEIC has a maximum period of 30 working days (46).

For CTs and studies that use medical devices, the committee of competent ethics (CEC) is CEIC, unless it designates an Ethics Committee for Health (CES) for this purpose (46). In other studies, the CEC is:

a) The CES that works in the center of involved clinical study; or

b) In the case of the clinical study center involved do not have CES, the CEIC or CES designated by it (46).

#### 3.4.2.3. CNPD

In Portugal, in order to conduct a CT, the sponsor must be seek a favorable opinion from the National Commission for Data Protection (CNPD). The CNPD deliberates to establish the general conditions for the processing of personal data in order to conduct clinical research (61).

CNPD has a legal deadline of 30 working days to reply to opinion requests (46). Not specialized in the clinical research area, the CNDP may need more time than other entities in the approval process (62). In addition to increasing the bureaucratic complexity of the approval process, this requirement has caused substantial and unavoidable delays in the start of CTs (62).

#### 3.4.2.4. Clinical Study Center

A clinical study center is an organization that conducts clinical studies, equipped with appropriate materials and human resources, regardless of their inclusion in health establishments, public or private, laboratory, or other, or their location or not in the territory of member states of the European Union (46). The clinical study center is responsible for determining the requirements for approval of financial contracts, and decide on the approval of these within 15 working days from the date of the request of the investigator or the sponsor (46). In addition, the clinical study center should provide data on the process of approval and implementation of the financial contract on the RNEC (46).

### 3.4.3. **Pharmacovigilance in Clinical Trials**

According to the World Health Organization (WHO), Pharmacovigilance is the science or set of activities related to the detection, assessment, understanding and prevention of AEs or any other problems associated with the use of drugs (63). Although most of the time pharmacovigilance is associated with Post-marketing surveillance of adverse drug effects in the fourth phase of CTs, the truth is that with the development and knowledge of drug mechanisms, pharmacovigilance is increasingly present in earlier stages of CTs of drugs (64). Based only on preclinical studies it is difficult to predict the side effects that may occur in Phase I CTs, and safety monitoring during CTs

is now a standard procedure and one of the major concerns for new drug development (64,65). During a clinical trial, the information about the AEs experienced is collected, assessed, monitored and reported to the sponsor and to the correspondent authorities (65).

In Portugal, the INFARMED is the authority responsible for the management and evaluation of notifications of Suspected Unexpected Serious Adverse Reaction (SUSAR), Annual Safety Reports and other safety information, in order to detect and assess signals of safety (58).

### 3.4.4. Clinical Trials in Portugal

According to the latest INFARMED statistical analysis, from 2011 to 2015 the number of approved CTs in Portugal by INFARMED has increased each year, as we can observe in Figure 2 (66). This increase was accomplished after many years of constant decrease in the number of CTs authorized by INFARMED. Although they have been increasing in the last few years, the number of CTs in 2015 (123 authorized CTs) have not reached the registered maximum of 147, a number that dates back to 2006.

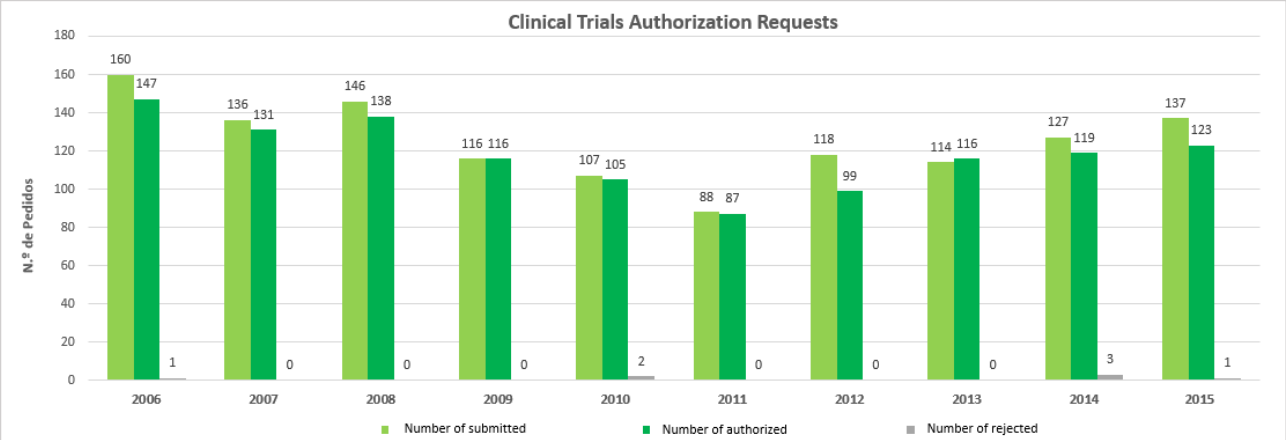


**Figure 2. Number of Clinical Trials authorized by INFARMED (Adapted from INFARMED** (66)**)**

Portugal has a really high quality of human resources, due to big investments in personnel training occurred in the past few years, and the CT sites have a strong connection with schools and universities, a kind of partnerships that is essential to some CTs and the investigation itself, when compared to other countries in Europe.

Even though, Portugal still has major barriers, like the negative reputation within the Portuguese population regarding to CTs, since people tend to see themselves as guinea pigs in a totally insecure experiment, and there is still a low impact of the clinical investigation in the investigator's professional valorisation (62). Also, the time of approval for CTs, that even though it has been decreasing in the past years, is above the European average, making it a disadvantage if the sponsor wants to quickly implement its trial in Portugal (62).

Saying so, it seems that Portugal really has no big advantages in what comes to the conducting of CTs. Although efforts are actually being made by the Portuguese authorities in regards of CTs, like the recent creation of *Plataforma Nacional de Ensaios Clínicos* (PNEC), Portugal must continue to follow the path of innovation, persistence and regulations in CTs area, at the risk of disappearing from sponsors' map (62,67).

Despite the new clinical investigation law, much can still be improved in what comes to the overall success of CTs. There is a need a governmental agenda that establishes a sound strategic plan for this sector. It should be created conditions in order for CTs to be performed in primary health care facilities (62). By doing it, recruitment and awareness for the importance of CTs could be improved. Also, a review of the role of clinical research professionals, and healthcare professionals who work in clinical research, is paramount. (62). Adding incentives to working in clinical research would motivate health care professionals to participate in clinical investigation, addressing one of the disadvantages mentioned before. This could also promote high quality standards in the clinical practice.

## 3.5. Pharmacovigilance

### 3.5.1. What is an Adverse Drug Reaction?

An ADR, in the pre-approval phases with a new medicinal product or its new usages, is any noxious and unintended response to a medicinal product related to any dose, meaning, due to any response to a medicinal product, meaning that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (68).

For marketed medicinal products, an ADR is considered a response to a drug which is noxious and unintended. It includes all conditions resulting from the use of a drug according to what is described in the Summary of Product Characteristics (SPC) or package leaflet (PL) as well as those occurring from a usage that is not in accordance with the described in the SPC and PL, as those resulting from medication errors, misuse, abuse, or resulting from occupational exposure to drug (69).

No medicine being effective is free of AEs. There are several ways to classify an ADR, and the classification presented below, achieved by Edwards et al. (70), is the most widely known:

ADVERSE DRUG REACTIONS

| Type of reaction | Mnemonic | Features | Examples | Management |
|---|---|---|---|---|
| **A: Dose-related** | Augmented | • Common<br>• Related to a pharmacological action of the drug<br>• Predictable<br>• Low mortality | • Toxic effects:<br>Digoxin toxicity; serotonin syndrome with SSRIs<br>• Side effects:<br>Anticholinergic effects of tricyclic antidepressants | • Reduce dose or withhold<br>• Consider effects of concomitant therapy |
| **B: Non-dose-related** | Bizarre | • Uncommon<br>• Not related to a pharmacological action of the drug<br>• Unpredictable<br>• High mortality | • Immunological reactions:<br>Penicillin hypersensitivity<br>• Idiosyncratic reactions:<br>Acute porphyria<br>Malignant hyperthermia<br>Pseudoallergy (eg, ampicillin rash) | • Withhold and avoid in future |
| **C: Dose-related and time-related** | Chronic | • Uncommon<br>• Related to the cumulative dose | • Hypothalamic-pituitary-adrenal axis suppression by corticosteroids | • Reduce dose or withhold; withdrawal may have to be prolonged |
| **D: Time-related** | Delayed | • Uncommon<br>• Usually dose-related<br>• Occurs or becomes apparent some time after the use of the drug | • Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol)<br>• Carcinogenesis<br>• Tardive dyskinesia | • Often intractable |
| **E: Withdrawal** | End of use | • Uncommon<br>• Occurs soon after withdrawal of the drug | • Opiate withdrawal syndrome<br>• Myocardial ischaemia (β-blocker withdrawal) | • Reintroduce and withdraw slowly |
| **F: Unexpected failure of therapy** | Failure | • Common<br>• Dose-related<br>• Often caused by drug interactions | • Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers | • Increase dosage<br>• Consider effects of concomitant therapy |

SSRIs=serotonin-selective reuptake inhibitors.

**Figure 3. Classification of adverse drug reactions according to Edwards et al. (Taken from '*Adverse drug reactions: definitions, diagnosis, and management*'** (70)**)**

How can we control and minimize the risks of an AE is the issue.

### 3.5.2. **Definition of Pharmacovigilance**

Pharmacovigilance is defined by the WHO as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem*" (71). It encompasses the identification of new potential ADR signals in real-life conditions - since not all ADRs can be detected in CTs - and post marketing safety surveillance activities to monitor drug benefit-risk rations (72).

A drug can only be marketed after it has been approved in phase I, II and III CTs (73). However, the detection of an ADR in a CT is limited and imperfect, due to the brief duration, an extremely closed monitoring setting, the exclusion of concomitant therapies and diseases, the restricted and highly selected number of patients, in comparison with the general population and the high compliance with the treatment by the patients (73,74).

CTs have difficulty detecting ADRs with long latency times or associated with prolonged use of a drug, ADRs resulting from drug interactions and ADRs that only occur in certain patients group. It is up to Phase IV CTs and pharmacovigilance systems to monitor the drug after it has been marketed. Thus, strict post-marketing surveillance is fundamental for the effective knowledge of drug safety profile (73,74).

### 3.5.3. National Pharmacovigilance Systems

The SNF was created in 1992 and it is constituted by the Drug Risk Management' Direction of INFARMED. In 1997 an evaluation was conducted by INFARMED, which revealed a very low reporting rate, reduced technical and scientific resources, failure to comply with the EU legal obligations and ignorance about the SNF (58,75). So, in 2000, to overcome the difficulties the SNF has having, the system was decentralized, to better approach health professionals, bring together universities to promote their technical and scientific expertise, improve the dissemination of the system and increase the notification (7,58,75). Four Regional Units of Pharmacovigilance (URF) were created from this decentralization: the North Pharmacovigilance Unit, the South Pharmacovigilance, the Pharmacovigilance Unit of the Azores (currently disabled) and the Central Pharmacovigilance Center (7,58).

Each URF promotes training activities among notifiers and assesses reports of ADRs that occurred in their respective geographical areas, which correspond to current health regions: the Northern health region (URF North), the Center (Center URF), the Lisbon and Tagus Valley (URFLVT) and Alentejo and Algarve (both belonging to South URF) (7,58). Its activities contemplate the disclosure of the Pharmacovigilance activity, in particular the reporting of AEs and the system itself, dissemination efforts among the general population, and participation in scientific projects (7,58,75).

### 3.5.4. Tools in Pharmacovigilance

No matter how well designed and conducted that are animal experiments, the fact is that human toxicity cannot be predicted with full accuracy, and there is not any animal model that can fully reproduce the ADRs that occur in humans (76). On the other hand, a patient in a CT is rarely exposed to the drug for periods greater than one year (76). Due to these limitations, CTs rarely detect or define the frequency of all important ADRs (76). Once the marketing of a new drug begins, there is a large increase in the number and type of exposed patients, including those with multiple pathologies and undergoing concomitant therapies, thereby increasing the likelihood of detecting ADRs.(76).

It can be concluded that the ongoing efforts of drug safety monitoring after marketing are essential and several methods can be used, among which the Spontaneous Reporting System (76). The Spontaneous Reporting System has been the main drug safety surveillance method used in Europe (76). This procedure allows the generation of hypothesis that, in many cases, need to be further investigated by epidemiological methods (76). Thus, the spontaneous reporting of AE allows an early detection of ADR not yet identified; identification of risk groups; obtaining reliable estimates of toxicity compared between drugs within the same therapeutic class; and a continuous monitoring of safety data (76).

Typically, the quantification of risk requires the execution of formal epidemiological studies to provide measures of frequency and valid and accurate associations (76). However, this is difficult, if not impossible, to be done with the speed required for pharmacovigilance activities, unless there are effective and validated information sources (76).

## 3.6. Medical Writing

### 3.6.1. Systematic Reviews

With the rising growth of available healthcare information everywhere, it becomes impossible for a health care professional keep up with every new on the field. Most important, it is difficult to select good quality information for every little thing that should be done in a daily basis. In this daily rush, health professionals need information, in an accessible and summed up format, that can provide robust research-based evidence on particular healthcare themes.

The aim of a systematic review is to present a balanced and impartial synthesis of all empirical evidence that fits pre-specified eligibility criteria, so a specific research question can be answered (77). The creation of a systematic review begins with a peer-reviewed protocol, stating the objectives and methodology of the article, so that the procedures of the review can be replicated if necessary. This is also needed in order to minimize bias, providing consistent and trustworthy information from which can be drawn conclusions and better and reliable decisions taken. Systematic reviews are very important for proper evidence-based medicine.

The production of a systematic review can be sliced in five parts: the definition of the question, the search for relevant information and evidence, the selection of the studies by assessing their quality, analysing the methodological quality of studies and summarizing the evidence, and finally the presentation of the results, with interpretation of findings (78,79).

Just like any other scientific research, a good systematic review requires a question or a set of well formulated, unambiguous and structured questions (78,79). It should contain the description of the disease or condition of interest, population, context, the intervention and outcome. All this must be defined before beginning the review work (78,79).

Researchers must make sure that all important papers that fit the inclusion criteria are included (78,79). The search for evidence begins with the definition of terms or keywords, search strategies and the definition of databases and other sources of information to be searched. The study selection criteria should be originated directly from the review questions (78,79). Multiple sources, both electronic and printed should be searched, and all the reasons for inclusion and exclusion should be recorded (78,79).

During the selection of studies, the evaluation of titles, abstracts or even the full article identified in the initial search should be made by at least two investigators independently and blindly, strictly observing the criteria for inclusion and exclusion defined in the study protocol (78,79). The inclusion and exclusion criteria are set based on the question that guides the review: appropriate search time, target population, interventions, measurement of outcomes of interest, methodological criteria, language, type of study, among others (78,79). Selected studies should be subjected to high quality assessment by use of general critical appraisal guides and design-based quality checklists (78,79). Disagreements that may eventually occur must be resolved by consensus (78,79).

The articles included in the systematic review can be presented in a table that highlights its key characteristics, such as authors, year of publication, study design, number of subjects, comparison groups, as well as use of statistical methods for exploring differences between studies and combining their effects (meta-analysis) (78,79). Information on the inter-rater reliability in assessing the evidence of quality should be presented, as well as the criteria used to resolve disagreements between them (78,79).

Exploration for heterogeneity should help determine whether the overall conclusion can be trusted, and any recommendations should be classified by reference to the strengths and weaknesses of the evidence (78,79).

Systematic reviews should follow the PRISMA statement. This consists of a 27-item checklist including items that seek for transparent reporting of a systematic review, in order to avoid a poorly reported article (80).

#### 3.6.1.1. Meta-analysis

Many systematic reviews also contain meta-analyses. Meta-analysis is a quantitative (statistical), formal, epidemiological study design used to summarize the results of independent studies (77,81). By combining information from all relevant studies about that body of research, meta-analyses can provide more precise estimates of the effects of healthcare than those derived from the individual studies included within a review (77,82). They also facilitate examinations of the consistency of evidence across studies, and the exploration of differences across studies (77).

# 4. Developed Activities

As proposed in the beginning by our co-advisor Professor Joaquim Ferreira, this internship has covered several different areas, allowing me to have the opportunity to work with different sub-units of the CPU and to communicate and work in a multidisciplinary environment.

The internship started with working in the outcomes sub-unit for two months. Afterwards, I moved to the UFLVT Sub-Unit for another two months. Later on, I've changed to Clinical trials Sub-Unit, which occupied most of the internship duration – 4 months; however I continued to work in projects related to medical writing that started at the outcomes sub-unit. In May, I started to work in an open workspace with the Biostatistics and Methodological Sub-Unit in the medical writing area.

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

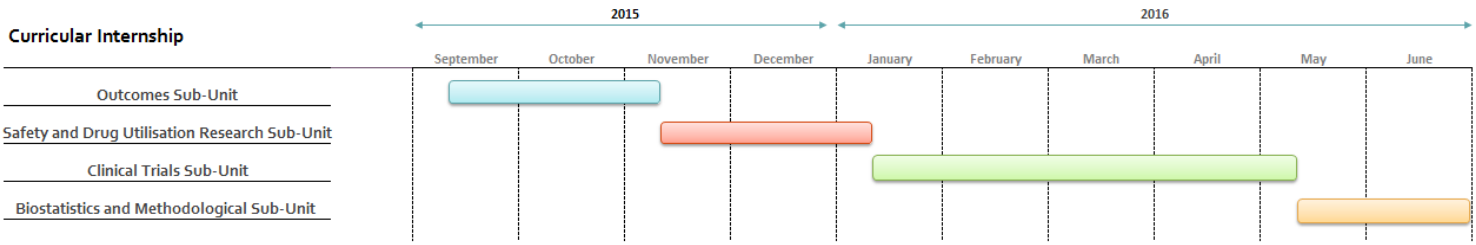


**Figure 4. Gantt chart with the schedule and duration of the internship activities**

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

## 4.1. Outcomes Sub-unit

As I mention above, I started my internship under the wings of Professor Ricardo Fernandes, a paediatrician on HSM, who is also a clinical researcher in the CPU since 2008. With him, I was mostly assigned to project management and medical writing activities, by being involved in his projects.

Shortly beginning work in this sub-unit, I helped in three main projects: setting up an OS, help one of his medicine students by writing with her one systematic review and write a scientific article on drugs in pregnancy.

The first project that was placed on my hands was ALFABETO, which was an observational, prospective, multicenter, with prognostic factors in children with acute bronchiolitis oxygen under high flow at different levels of care. In the first week I had to know all documents created for the project, such as protocols, case report forms (CRF), scales, documents for submissions, among others.

My first task with this project was to submit the study to CNPD. To this end, I consulted the electronic form submission of CTs and OS, as well as the database of previous decisions by the

CNPD for OS in the country, to understand what the CNPD asked in their submissions, and what are the most sensitive issues, in order to better defend the purpose of our OS.

Then I was asked to make improvements to the protocol and review and improve the CRFs. To accomplish this task it was necessary to go back to look at the guidelines for GCPs, so that all required points were integrated into the normal OS procedures.

When this task was finished, we realized that it would be necessary to make some standard operating procedures (SOP), so that certain tasks were standardized. SOPs are documents which provide written instructions how to conduct a given procedure, to ensure that it is conducted in uniformity by all members of an organization. My job was to write two SOPs, being always in contact with Professor Ricardo Fernandes, so that the SOPs were faithful and clinically reliable to what was going to happen in the study.

Also, I was tasked with creating a database on Excel in order to, once the study started, introduce paper CRF data and source document data into the electronic CRF (eCRF). For this, I had to analyse the CRF in detail, in order to understand what information was needed to be drawn from this. It was also necessary to understand how to use the Excel's tools and formulas in order to get the best of them, adapting them to the needs of the study. Afterwards, this database will be analysed by statisticians, with the purpose of obtained the results and statistics of the OS, so that a conclusion can be drawn from medicinal products under study.

The second project was to write a systematic review on children with chronic disease in paediatric CTs. This project was the final thesis work of a medicine student. With this systematic review we aim to evaluate how many children with a chronic disease are being excluded from acute bronchiolitis' CTs. This is an important theme to discuss and shed light on because children with chronic disease are the most affected by this disease, and if they are being excluded from these CTs, then there are no sufficient information about the treatments for these diseases in this population. This could be a serious lack of information about an already fragile and sensitive population.

My and my colleague Raquel Rodrigues' contribution is systematized in the following figure:

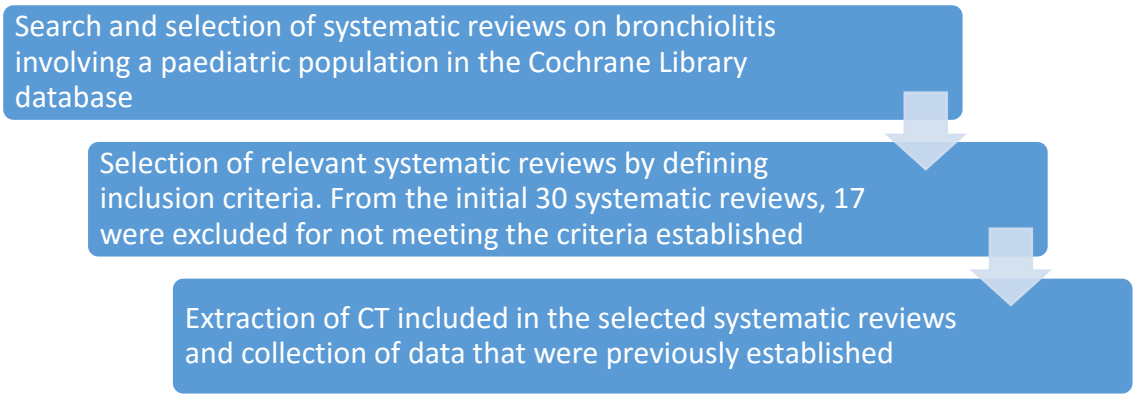


**Figure 5. Contribution on the development of the systematic review "Children with Chronic Diseases in Paediatric Clinical Trials"**

With this systematic review, we concluded that clinical decisions for the paediatric population with acute bronchiolitis has been made based on old, outdated reviews, with comparisons of interventions that are no longer used. As for the number of children included, we observed that, as would be expected from a fragile population, the numbers are not big, and further lower the including children with chronic diseases. Moreover, having chronic conditions such as prematurity and cardiopulmonary chronic conditions, diseases known to be risk factors for a more severe outcome in bronchiolitis, are exclusion criteria for entry into many, if not all, CTs.

Thus, it can be concluded that there are not being prepared treatments for the real target population of bronchiolitis, and that patients who can most benefit from scientific studies in this area are not being included in well-designed CTs, with well-defined criteria and with the rigor that is needed in these studies. By changing this scenery, we can get more reliable results that are better suited to the current clinical practice.

The third and ultimate project was to write a reflexion article on drugs that can be taken during pregnancy and breastfeeding. There is a huge lack of knowledge in this area, and me, Professor Ricardo Fernandes and Dr. Ana Marta were interested to investigate the knowledge that we have of drug effects on pregnancy, which medicaments can be taken and which should be avoided, and the state of the current legislation in the world and in Europe.

After conducting a database search for articles with the relevant keywords, some articles relevant to the article were found. A skeleton of the article was designed and an attempt was made to start writing the article, but this project was put on standby due to other activities deemed more relevant.

## 4.2. Safety and Drug Utilization Research Sub-Unit

After the first phase of the training in project manager had been completed, I moved to UFLVT' room. Here, I started my training in pharmacovigilance with an introduction about the area, some

instructions by Dra. Ana Augusto, the quality manager in the UFLVT, and with some reading on scientific literature and guidances.

Once the introduction was done, I started to become familiarised with the QMS and its documentation (quality manual, processes, procedures, work instructions, document models, and records). With this, I started to understand how a company can be guided and organized by quality and standards.

As soon as I become comfortable with the procedures and concepts related to pharmacovigilance and quality assurance, I was able to collaborate in the daily activities of UFLVT. The main task that the collaborators of the UFVLT have to have in mind is that the mission here is to protect and improve public health.

The UFLVT has three groups of basic activities: processing and ADR's analysis, dissemination and promotion of the reporting of suspected adverse reactions in their geographical area and communication to INFARMED of suspected adverse reactions that they receive. Based on these activities, UFLVT has a set of objectives, including 250 notifications per million inhabitants per year, which equates to about 900 notifications a year, and 60% of these should be serious ADR. There should be less than 5% error in the handling of these notifications, and they must give at least six dissemination/training events. From the results obtained and analysed from the 2nd semester of 2015, it can be concluded that these objectives were met.

Some of the responsibilities of the unit include the collection, management, and assessment of medicines safety data, which can also include the detection of irregularities in the data and to trigger safety warnings upon the evidence of ADRs. In order to know all the steps by which a notification of an adverse reaction goes through in this unit, I spent some time at every stage so that I could understand why they are needed, learning who they are doing and to be able to redo them later.

A spontaneous notification of an ADR can arrive by many forms: fax, mail, e-mail, telephone or by the portal. The first task is to understand if the notification can be considered valid. For a notification to be valid, the report must include four essential criteria: a symptom or a signal of an ADR; the active substance that is under suspicion of being the cause of the ADR reported: an identification of the notifier, that can be any person; and an identification of the patient. If any of this information is missing, and after several attempts to get the essential data, it is not possible to meet the minimum criteria with the notifier, then the notification is not processed by the unit. On the other hand, if the notification has these four minimum criteria, it can be assessed by the collaborators of the UFLVT.

The report will be signed, dated and a temporary number will be assigned to it. If the notification is not received by telephone, efforts will be made to confirm the existence of the notifier and to

collect any additional information that may be needed to white the initial report, either by phone call, e-mail or letter.

If the notification was not received by the Portal, it has to be inserted in it. Then, the case will be sent to SVIG, the database of SNF, and attached with a copy of the original report, provided by the notifier. Also, a reply is sent to the notifier with confirmation of data reception and acceptance of the report.

Afterwards, the case must be assessed by the medical coordinator through the analyses of the SPC and the periodic safety update reports of the medicine, so a causality category can by assigned to the notification, which is posteriorly included in SVIG. The categories of causality of an ADR are the ones provides by WHO, and they include six categories: certain, which means that ADR occurs in a plausible time relation to drug administration, cannot be explained by other drugs or underlying diseases and normally requires a reexposure procedure; probable/likely, when a ADR have a reasonable time relation to administration of the drug, and does not require reexposure information; possible, meaning that although there is a reasonable time relation to administration of the medicine, the ADR could also be explained by other concomitant drugs or underlying diseases; unlikely, when a ADR has a temporal relation to the administration of the drug, which makes a causal relation questionable, and in which other concomitant drugs or underlying diseases provide more plausible explanations; conditional/unclassified, when an ADR needs more data for a proper assessment or the additional data are being examined; and unassessable/unclassifiable, which occurs when an ADR cannot be judged, since information is insufficient or contradictory and it is impossible to be verified or supplemented (70,83).

If the ADR is not described on the SPC, then it must be searched on the existing scientific publication. The UFLVT does this search on the PUBMED search engine, by search the association of the medical dictionary for regulatory activities (MedDRA) term in English with the active substance of the medicine that is suspected to cause the ADR. If any information in any article is found, this must be reported in the causality report. Furthermore, a written summary report about the case with all the information needed will be attached to the original notification and will be archived in the UFLVT archive. The notifier will receive a letter with information about the causality category that was attributed to the notification reported, as well as indication on whether the ADR was described or not in the SPC. For all pharmacovigilance data and documents for each authorized product, they must be preserved whilst the product is authorized and for at least 10 years after the introduction of the marketing authorization has ceased to exist.

## 4.3. **Clinical Trials Sub-Unit**

The internship on Clinical Trials Sub-Unit began in January, after two months on UFLVT. During the four months I was assigned there, I worked under the close guidance of Dr. Ana Noronha and Dr. Ana Salgueiro, the SCs of the research centre, as a clinical research coordinator. A SC has a strong role in facilitating, supporting and coordinating the daily CT activities and in the conduct of clinical research under the supervision of the principal investigator (PI). By executing this functions, the SC works along with the PI, the sponsor, the monitor and the institution to provide and support guidance on the compliance, financial, personnel and other aspects concerning the clinical study (84).

In the first week I received a full overview of the CT site, the procedures in place, where the material was stored, the general workflow of the centre, the hierarchical structure, who were the different PIs of each trial, amongst many others.

I quickly realized that this highly specialized field demands different and competent individuals to work in team, being a multi-disciplinary work force. A usual clinical research team comprises the following team members:

- PI and sub-investigators, who are physicians with knowledge in GCP, experience in conducting CTs and have training in the specialized field that is under study of the CT. They are responsible for selecting and recruiting participants, prescribing and administering the investigational product, supplying the medical care needed to CT subjects and ensuring the safety and well-being of them is maintained during the trial. Also, they are responsible for answering any queries that may appear during the trial, raised by the monitor or the sponsor.
- The Clinical trial coordinator who, as explained above, works along the investigators, and is responsible for conducting the study in accordance with GCP, the protocol and ethical standards. Being a multitask role, the CT coordinator is assigned with administrative tasks, handling financial aspects, preparing important documents, monitoring the procedures or even collecting data; in general, this professional eases the entire research process, acting as the connecting point between all research team.
- The study nurse(s), who is responsible for collecting biological samples from the CTs participants, as well as providing guidance and support to patients and study team.
- The hospital pharmacists, who are responsible for receiving, storing, dispensing and for the accounting of the investigational product.

Despite this job may already be somewhat standardized in the course of CTs, the duties and responsibilities of a SC may vary across different infrastructures. During my internship here, I gained knowledge and learned many assignments that are universal to most CTs, like the compliance with

the procedures stated in the protocol, archiving and filling eCRFs, measurement of vital signs and processing of laboratory samples.

After my initial training in the tasks mentioned above was concluded, I was in a position where I could start being a part of the larger activities in place at the site. Many trials were ongoing when I started the internship, and some of them started during the internship. The initial training was essential for me to do an efficient work on the CTs specific activities, such as the preparation of patient appointments and answering queries. Although each trial was different, there are many features that are the same for all of them.

What follows is a list of the procedures where I received training during the internship.

### 4.3.1. Compliance with the protocol and the procedures

One of the most important goals to ensure throughout a CT is the compliance with the investigation protocol. Before any trial procedure, the protocol must be read with the upmost attention, in order to understand the objectives of the trial, the needed evaluations and the study's procedures. When the date of a visit approaches, we should always come back to read the protocol in order to know what procedures should be carried out, by whom and in what order, so that all proceedings and all indications are taken into account and prepared in advance.

### 4.3.2. Measurement of vital signs

Most of the trials occurring in the centre required the measurement of vital signs in several schedule visits. I received training by Dra. Ana Noronha and Dra. Ana Salgueiro in measuring temperature, blood pressure, pulse, respiratory rate and weighting, and once I learned how to handle with the equipment and perform the tasks correctly, I was allowed to do these simple procedures whenever the protocol required.

### 4.3.3. Processing laboratory samples

Being in a CT environment, in some scheduled visits it is required to collect biological samples, such as blood, tissues and urine. As so, in order to do that, each study sponsor provides us a laboratory manual with precise instructions on how to collect, handle, process and ship the required biological samples. In our research centre, we only work with blood and urine samples.

In order to help with this important task, Dra. Ana Noronha and Dra. Ana Salgueiro taught me how to correctly handle with the particularities of each laboratory kits of each trial, how to work with the centrifuge to process the samples according to what is specified in the laboratory manual, and

prepare each sample to be shipped to the central laboratory, either in ambient temperature or in dry ice.

### 4.3.4. **E-CRFs**

Due to be multiple CTs ongoing in the center, I had to learn to fill out different eCRF's provided by the CTs sponsors, so that it can be inserted online the data gathered in source documents (paper) of the CTs. Each eCRF had its own design, layout, specifies, and peculiarities. Usually, if the CT involved more data to be gathered, the eCRF is more complex than others. Some ones were very intuitive, having a friendly user interface, but others required a long time to be filled and had some bugs that we had to ask for IT team to solve.

During the internship, I had to learn how to resolve queries, like simple ones, who were usually transcriptions errors and quick to solve, and more complex ones, like questions raised by the monitors and data managers related to inconsistences or incoherencies, that required a team effort amongst physicians and SCs to be solved.

It was also made very clear during all training that confidentiality was a very important issue when accessing the different eCRFs.

### 4.3.5. **Archiving**

In order to maintained organization in the center, each study had a specific cabinet, where their documentation was safely archived. Each cabinet had a specific organization, mainly decided by the monitor, but the basic features were similar for every trial, like patient dossiers, where all documentation of a CT participant is kept, and the investigator site file (ISF), an enormous file where all information concerning the CT is available, including the investigator brochure, the study protocol, contact information, financial agreements, study manuals, important communications between sponsor and vendors, information on AEs, SUSARs and much more.

The organization is very important in CTs due to the tremendous workload and paperwork, which creates a lot of opportunities for confusion and wasted time looking for specific documents, not to mention the risk of loss or misplacement of documents. It was of the upmost importance to keep everything organized, in place, and readily available. If a document is lost, it means that data is gone and can never be recovered. This is much frowned upon the trial sponsor, since it shows that the clinical research center may have organizational problems, and leads to a higher number of monitor visits.

### 4.3.6. **Conducting a Clinical Trial -** Trial specific activities

#### 4.3.6.1. Feasibility phase

The feasibility phase is designed to select potential sites and PIs. This occurs when the sponsor asks the PIs about their interest in conducting the CT. Then, a feasibility questionnaire is delivered and the PI and SCs must fill it in. The questionnaire has the objective of evaluating the clinical research centre conditions and the PI availability.

When the PI has interest in conducting the CT, some information must be provided, such as the site experience in clinical research, the target disease, resources and facilities available, and who the person of contact is, in case of additional questions.

If the sponsor agrees with the implementation of the CT at the research centre, the next step is a face-to-face feasibility visit. In this case, the meeting is between a representative of Contract Research Organization (CRO)/sponsor, the PI and SC. During this meeting, the PI signs the confidential agreement and then the study protocol (or a small version of it) is presented for the first time. Then, the PI has the opportunity to give his/her opinion, discuss the protocol and the inclusion/exclusion criteria, or any other ambiguous question. There are some topics that are usually discussed, like the number of patients that should be recruited, the financial contract, and the approval timelines from the Administration Board of the CHLN, E.P.E. – HSM and the Ethics Committee.

#### 4.3.6.2. Investigator's meeting

The purpose of these meetings is to train and motivate research teams to meet the challenging demands of the protocol as well as to recruit the large numbers of patients that are essential to its accomplishment. On these meetings, it is very common to have the whole team involved in the CT, like the investigators, SCs, raters, monitors and quality assurance and senior managements. The most important investigator meetings happen before the trial begins, although other meetings could be planned during the ongoing study.

#### 4.3.6.3. Site Initiation visit

I was allowed to see two trial initiation visits during my internship. These are formative events conducted by the monitor and the trial sponsor to prepare the research center for the proper conduction of a trial, drawing attention to every detail and all possible problems that may arise, and how we can solve them. The entire research team is reunited, including SCs, investigators, raters and nurses. In these meetings the monitor, in representation of the sponsor, provides a presentation on the CT, giving an in-deep look to the investigational product characteristics; at the Investigator's Brochure and the protocol, focusing on its goals and procedures; to the inclusion and exclusion

criteria, the Informed Consent Form (ICF) and all the informed consent process; all the source documents used in the CT, where the trial specific information is collected; to the CRF; to the ISF; to the possible AEs and serious adverse events (SAE) and how should they be reported; and to the monitoring requirements and how frequently can they occur.

Throughout this visit, it is given space and time to the research team to ask all their questions regarding the trial that they still have, in order to make to most of the rare occasion that is a reunion with the sponsor of the trial and all of the site staff. Typically, after the initiation visit has been concluded, the site is ready to start recruitment, although in most cases the recruitment is postponed until trial essential equipment arrives at the site.

Also, the PI is requested to be available in order to discuss the Investigator's Responsibilities. Typically the investigator delegates some of the responsibilities to others (i.e. sub-investigators, SCs…) but ultimately, he is the person responsible for all actions and for conducting the study. To ensure everybody knows his/her roles and responsibilities, each task is written in the delegation log which is kept in the investigator site file. Regarding regulatory obligations of each member of the team, some training activities are also scheduled, in case they were not performed in the investigator's meeting or are no longer within the validity period (such as training in GCP, which should be performed frequently over the years).

#### 4.3.6.4. Patient recruitment

The only way possible in Portugal to find participants to the studies that are currently developing in our research center is through the investigator, where a patient first comes into contact with a CT owing to the fact that its physician is a PI or a sub-investigator of a study. This method relies on the patient population of the physician/site and the efforts of the investigator and their staff in identifying potential patients and enrolling them in the study. It is also common to contact previous patients from another trials.

When a patient is identified as a possible candidate for a CT, usually in the outpatient clinic of Neurology in HSM, the investigator introduces the trial to the patient and delivers a copy of the ICF to the subject, giving the patient the opportunity to decide with his/her family if the CT meets their expectations and if they want to accomplish it. After this first approach, another visit or a phone call is scheduled, to know if the patient is interested to take part in the study, so that the screening visit is scheduled.

#### 4.3.6.5. Preparing patient appointments

Whenever the day of a patient appointment approaches, it is essential to study core assessments of the visit and recall the previous visits and history of the patient. Also, a phone call should be made to remember the patient of the day of the visit and to come fasted (if applicable) and to bring his patient diary (also if applicable).

A day or two before the visit, all the required material for the visit must be gathered. These include the patient's medical file, the interactive voice response system (IVRS) or interactive web response system (IWRS) sheets, pharmacy prescription forms, vital signs form and source documentation. We also prepared the laboratory tubes, pre-labelling them with the patient's identification, and all the equipment required, like a thermometer, a sphygmomanometer or an electrocardiograph. If we have biological samples to be shipped on dry ice, we also would ask for it to the laboratory.

Checking the laboratory material was also a common procedure, to ensure that the center was well stocked for the upcoming visits.

#### 4.3.6.6. The day of the appointment

If it was a screening visit, the effort of a SC is focused on providing support to the PI in the informed consent process, while the investigator explained the medical and scientific background of the trial, referring all the medical evaluation that the trial will require. The SC is tasked with answering logistic questions that the patient and the companion/caregiver (if applicable) may have, such as where the visits and required examinations will be carried out, how was transportation and food expenses will be handled, and precautions to have with the patient's diary (if applicable).

In treatment phases visits, after the investigator signed the pharmacy prescription, I would complete the IVRS (or the IWRS) and then would send to the pharmacy through e-mail.

If it was an ambulatory treatment, I also received the returned medication, checked the patient's compliance with the therapy (usually through the patient diary, or by counting blisters) and then return it to the pharmacy. While the investigator evaluated the patient or the raters applied their scales (if applicable), we waited for the medication that usually came 20-30 minutes after the request. Once at the centre, the investigator delivered the medicine to the patient, and provided instructions on how to take it. Details on the next appointment would also be provided.

If it was an intravenous treatment or an injection applied by nurses, after being evaluated by the investigator and then applied the scales by raters (if applicable), the patient would have to go to the nurses' floor in order to receive the required treatment. If it was necessary measurements of vital signs, I and the nurses would measure it.

If the visit required the collection of biologic samples, a nurse would collect the blood of the patient according to the laboratory specific study procedures, and if required, the blood was processed. This usually meant giving some time to pass for the blood to clot, and then centrifuging the tubes. After centrifuging was over, the plasma would be transferred to the transfer tubes. Some trials required smear preparations to be done, while others required urine samples, which either the patient would bring it to the visit, or would be collected at the research centre.

Once all samples were processed, they were prepared for shipping in the proper boxes. For visits which required samples to be sent in dry ice, as I said above, I would request it them in advance, in order to have it arrived at the same day of the visit. Once the shipment was ready, the courier services would be called to schedule the pickup.

For patient expenses, the research centre asked patients to bring receipts of them, so that we could reimburse them. All this receipts were then be digitized and sent to the study monitors so that the site was later reimbursed for this cost.

All procedures performed by me had the supervision of the SCs of the research site, in order to ensure the conformity of data and compliance with GCP.

#### 4.3.6.7. When the visit was over

When the visit ends, all source documents must be reviewed, in order to ensure that all necessary data has been collected, and then this information must be entered it on the eCRF.

If an electrocardiogram was done on the visit, it must be sent to the central laboratory for evaluation, usually by telephone line. All material used has to be archived properly on the patient's folder.

Usually, after filling the eCRF with the collected data, some queries eventually appear. Prompt resolution of queries is an important objective of the center, as clinical trial sponsors place a high value on prompt query resolution. For queries where the answer was in the source documents, or if it was a misunderstanding or a transcription error, I would answer right away. If it was something related to clinical information or questions related to the patient, I would usually contact the investigator or the concerned health professionals, asking for clarification.

If any AE was reported, all forms have to be filled, and depending on the seriousness of the situation, we could have deadlines to meet, such as in a SUSAR situation, when we have 24 hours after becoming aware of the event to inform the sponsor. Following the initial contact with the sponsor, an expedited reporting has to be sent in 7 days (fatal or life-threatening SUSAR) to 15 days (all other SUSARs).

#### 4.3.6.8. Periodic monitoring visits

The primary goal of these visits is to make sure the CT is conducted, recorded and reported in accordance with protocol, GCP and SOP's requirements without compromising patients' safety and data accuracy. A monitoring plan is developed by the sponsor and/or CRO which includes the frequency and duration of periodic monitor visits; this plan is usually presented in the site initiation visit and the frequency of visits also depends on the performance of the research center throughout the study.

Usually, the clinical monitor sends an email describing the visit´s goals. This allows the study documents to be organized and reviewed in advance. The purpose of these visits is to evaluate the way the study is being conducted and to perform source document verification, in order to resolve all pendent queries. The monitor also ensures the data is completed, reliable and processed correctly. These visits can occur every few weeks or once a year and can take less than one day or up to several days at a time, depending on the number of patients, the complexity and the risks of the study.

#### 4.3.6.9. Site Close-Out Visit

On this visit, the research centre must ensure that all subjects have completed all visits. Then, all site data for all subjects have to be entered in database/CRFs, and that all information about AEs are recorded and followed up to resolution in accordance with the procedures detailed in the protocol. Also, it must be confirmed with the monitor that all queries are considered to have been resolved/closed. The Trial Master File review should be completed and ready for reconciliation by the monitor at the close-out visit. Also, it is necessary a notification from the sponsor indicating that the site is approved for close-out visit. Finally, all trial documents without identification of the patient must be archived in the hospital file, so that they are accessible for the fifteen years after the date of site closure required by the authorities, after which time the material may be destroyed.

### 4.3.7. **Other Clinical Research Centre activities**

Due to the fact that sponsors/CRO usually made contracts with other entities to perform the complementary exams or just to ensure the patients' transportation, I had to be in constant contact with these external clinicians, central group and company of transports.

I also had to perform some quality management' activities, in order to ensure the proper conditions of the studies' material. These included verification of the validation date of the material used, such as laboratory kits, and checking if any study material, like urine collection cups, were missing, so we could order more.

### 4.3.8. **Multiple Sclerosis Clinical Trials**

During my internship at the clinical trials unit, I was CT coordinator trainee responsible for the Multiple Sclerosis (MS) CTs, under the close supervision of Dra. Ana Noronha and Dra. Ana Salgueiro. During my initial training, I started studying the protocols and having a deep-look at the ISFs from the MS studies, like the ORATORIO trial.

MS is an inflammatory and degenerative demyelinating disease of the human central nervous system (85). This loss of myelin forms scar tissue (sclerosis), which gives the disease its name, resulting in a disruption in the ability of the nerves to conduct electrical impulses to and from the brain, producing a wide variety of symptoms (85,86). This disease manifest as neurological deficits referable to damage to the spinal cord, brainstem, optic nerves, cerebellum, and cerebrum, being accompanied by weakness, pain, visual loss, bowel/bladder dysfunction, and cognitive dysfunction (85). The diagnosis of MS typically involves the application of highly structured diagnostic criteria that rely on clinical observation, neurological examination, brain and spinal cord magnetic resonance imaging scans, and cerebrospinal fluid studies (87).

This global disease affects an estimated 2.3 million people worldwide, including approximately 630,000 in Europe, affecting at least two to three times more women than men (85,86). MS is clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS) (88).

PPMS is a relative rare form of MS, accounting for approximately 10-15% of all people with MS, being characterized by a progressive course from disease onset without superimposed discrete clinical attacks or relapses (85,88). No treatment has been demonstrated to significantly slow the progression of disability in patients with PPMS, including therapies approved for the treatment of relapsing forms of MS (85,88).

#### 4.3.8.1. ORATORIO Trial

Ocrelizumab is a humanized antiCD20 monoclonal antibody that targets mature B lymphocytes (85). This helps to supress the immune response and reduce the damage to myelin that occurs in MS. Results from a phase II trial of ocrelizumab versus placebo in patients with RRMS showed that both doses used were more effective than interferon beta-1a in reducing the number of brain lesions (85).

The ORATORIO trial is a phase III, multicentre, randomized, parallel-group, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with PPMS. I was responsible for preparing the centre for the open label phase of the study, when the patients in

both groups (placebo and ocrelizumab) are given the opportunity to receive ocrelizumab treatment in an open label fashion (89).

In order to prepare the centre for the open label phase, I had to organize the patient' passage to the main study to the extension phase. Since the treatment involved 2 infusions separated by 14 days in each treatment cycle, it was necessary to reconcile schedules of different members of the research team, including the PI, nurse, raters and other physicians involved in the assessments, such as MRI. This passage to the open-label involves the closure of databases, the prompt response to multiple queries that appear, and verification that all required information to be introduced into eCRF is there. Also, concomitant medications should all have been entered in the clinical database and reconciled with medical history forms and/or AE forms, as appropriate.

Owing to the fact that the promotor, Hoffmann–La Roche, submitted the drug for approval to the FDA, the research center had to prepare to receive a possible audit by part of the US official, verifying that all documents and all information was correct and inserted in the right places.

### 4.3.9. **Other trials**

| ***Trial*** | **Brief Description** | **Phase** |
|---|---|---|
| *EXPAND trial* | A multicenter, randomized, double-blind, parallel-group with the purpose of exploring the safety and efficacy of Siponimod (BAF312) versus placebo, in a variable treatment duration in patients with SPMS (90). | Phase III |
| *PROTEC trial* | A multicenter, open-label study evaluating the effectiveness of oral Tecfidera™ (Dimethyl Fumarate) in subjects with RRMS in the real-world setting (91). Tecfidera is the novel oral first-line treatment for RRMS by Biogen, which is now available for the Portuguese patients. | Phase IV |
| *MARGUERITE RoAD Trial* | A multicenter, randomized, double-blind, placebo-controlled, parallel-group study that evaluate the efficacy and safety of gantenerumab in patients with mild Alzheimer disease (92). | Phase III |
| *EPOCH trial* | A randomized, parallel-group, double blind to assess the efficacy and safety of verubecestat (MK-8931) compared with placebo administered for 78 weeks in the treatment of Alzheimer's Disease (93). | Phase III |

**Table 2. CTs in which I have contributed**

Table 2 provides an overview of other clinical studies to which I contributed to in one way or another.

## 4.4. **Biostatistics And Methodological Sub-Unit**

At the end of the internship, I returned to the Clinical Pharmacology Unit, in the third floor of HSM, in order to start to work with the Biostatistics and Methodological Sub-Unit in clinical data management and medical writing.

My first task in this unit was to help in an application for a research grant. In this research Grant, the University of Lisbon (ULisboa), with the support of *Caixa Geral de Depósitos*, assigned twenty annual "Scientific Awards University of Lisbon / Caixa Geral de Depósitos", to reward scientific research activity and encourage the practice of publishing in international journals of recognized quality.

For the application, it was necessary to deliver some documentation, including articles published by Professor Joaquim Ferreira in the past five years as well as the impact factor for all of them. For this, it was necessary to learn how to work with the Web of Science database and search engine, which is an online subscription-based scientific citation indexing service que provides a comprehensive citation search. I had to improve my quality of research and detail observation, so as to reach a list of articles with the necessary characteristics. Then, it was necessary to look for the impact factor of each journal, in order to gather all the required bibliometric data. With all this information reunited, the CPU was able to apply to the grant on time, and we're still waiting on answers on it.

I also had the opportunity to work with Dr. Daniel Caldeira, a cardiology physician who is also a clinical researcher in CPU. One of the themes that he was interested to explore was the safety of the new generation of anticoagulants. For that, I helped with two articles.

The first one, "Safety of non-vitamin K antagonist oral anticoagulants - coronary risks", I've worked early on the internship, by helping on manuscript preparation and data collection for this article that was latter submitted and accepted in Expert Opinion on Drug Safety. My assistance was recognized in the article acknowledgments.

The second one, "Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: a systematic review with meta-analysis", I was actively involved in it in the beginning of the internship, but most of the work occurred in the end of it. When the project was put in my hands, the idea for the article was already established, and the research on the databases had already occurred. My help was then needed on the selection of the articles, with the inclusion and exclusion criteria previously defined by Dr. Daniel Caldeira. Since the filtering of the articles was a two-person job, I was able to work with the software ENDNOTE alongside Dr. Daniel Caldeira. Through this software, we could easily manage hundreds of references, and filtering them was an easy task.

The next steps, like data collection and interpretation of results were made by Dr. Daniel Caldeira. My help was needed again in the final part, helping him by reviewing the article, helping

in the cover letter writing and article formatting according to the journal's rules, chosen for publication and on preparing the article for submission.

## 4.5. Courses and Lectures

### 4.5.1. Journal Club

Every Wednesday morning, the investigation team members of Neurological Clinical Research Unit and physicians of neurology gathered at 8 am to attend the clinical research centre's Journal Club. In these meetings, one member of the team was assigned to bring a recent article in the field of neurology and neurosciences, and then had to explain it and describe the study's findings to the rest of the team. A short discussion usually followed, ranging from considerations on the design of the study, the potential therapeutic applications of the findings, amongst other relevant topics. These discussions were particularly enlightening, as they showcased the group's dynamic and different backgrounds, and what prospects these studies could bring to the activities of a research centre. In addition to serving as a time to exchange information and share knowledge in the neurology field, these meetings also served as an opportunity for the site staff to talk in person to each other.

### 4.5.2. Afternoon Wednesday meetings

Every fifteen days at Wednesday afternoon, a meeting was held on the CPU with all members of the team. In these meetings, a different team member would bring forward a presentation regarding a project that they were working on. This helped the team members get to know what everyone is working on, discuss the project or idea of a project, provide feedback and opinions, or just show the results of their labour.

These meetings were very informative and a great learning method, since the discussion that was generated around the presented subject usually focused on the negative points and how to improve them, taking us to learn from the mistakes of others and how to fix them.

### 4.5.3. Courses

During my internship, I had the opportunity to attend some additional courses. These provided me with extra training and knowledge that were quite useful during the internship. I received three additional courses, one concerning GCP, another on quality, and the last one was an intensive course on pharmacovigilance.

#### 4.5.3.1. Pharmacovigilance Course

From November 16 to November 19, I attended an intensive course on pharmacovigilance at the HSM. The course provided an overview on the different reporting mechanisms of ADRs, how can we evaluate the risk-benefit of a medicinal product, what are pharmacoepidemiology studies and their purpose. The course also provided an overview of the SNF and its story and of the pharmacovigilance systems employed in other countries. The course then gave a rundown of the AEs that are more common for the different anatomical main groups, and which drugs are more associated with that AEs.

#### 4.5.3.2. Quality Course

At December 3th, 2015, I attended a quality course at *Instituto Português da Qualidade* (IQP), during my time at the Regional Pharmacovigilance Unit. This was a basic quality course, which gave an inside look on some of the norms regulating quality in several areas, such as CTs and pharmacovigilance.

#### 4.5.3.3. Good Clinical Practices Course

On December 4th, 2015, I attended the GCP workshop, organized by the CPU. In this course we were given an historical background of ethics in human research, starting with the Nuremberg Code, the document that started with all, to the different versions of the Helsinki Declaration that have appeared through the years. The GCP principles were detailed with dilemmas such as patient compliance, informed consent and the different interpretations of the GCP applied to different actors, like the investigator, the research team, the monitor and the sponsor.

This course was an excellent supplement to the knowledge obtained in the bachelor and master's degree, giving me more background, knowledge and confidence to deal with the CT coordination activities and understand the environment around the CTs world.

# 5. Discussion

Clinical research has changed the face of modern medicine, enabling, since the end of World War II, numerous possibilities of treatments that were only possible due to the improvements in the ability to effectively treat or prevent diseases. These successes had and continue to encourage the public enthusiasm for research and belief in clinical research.

This high quality of medical care is built with the contributions and efforts of many investigators and health professionals that dedicate much of their time in clinical research, in particular CTs. CTs are the current gold standard for demonstrating to the scientific community the safety and effective evidence concerning a new medical product.

Working in a CPU gave me the chance to have a broader vision of a clinical research project's lifecycle, from testing the drug in CTs to monitoring the safety of the drug through pharmacovigilance, and the production of scientific papers that seek to offer a summary of the current state of knowledge of a topic,. Due to the internship involving different departments with multiple professionals from diverse academic backgrounds, it allowed me to interact with different areas related to clinical research and CTs and understand how they can work together towards the improvement of the clinical and scientific knowledge for improved health care of the population.

By doing this report, I was able to understand and systematise the background information related to the areas that I have worked with during my 9 month training. However, a simple description of all the projects and major activities that I was in does not demonstrate the effort, difficulties, acquired skills acquired and outcomes of this on-the-job training, that are impossible to properly convey in writing. Nevertheless, this training, this work experience, the achievements gained, the professional contacts and connections made, and the professional and personal growth have made this internship an extremely challenging, but also an extremely rich experience.

Since the beginning of my curricular internship that I began to appreciate the effort for study procedures to be strictly followed and documented. CTs are extremely demanding for any professional who works on them, and one gold rule in CTs is "what is not written, it is not done". This require to all the individuals to be organized, to pay careful attention to the protocol, and to have an eye for details. Also, contacting with different kind of patients and health professionals requires a special sensibility, which should be adapted depending on their education, literacy and mental health, always in a scientifically correct manner.

The team working at CPU, in the in the various sub-units, are always in a constant effort to perform their work in the most efficient manner, making their balance and organization achievement truly impressive. All of these professionals, including physicians, study-coordinators, statisticians, psychologists, nurses and pharmaceuticals contributed to my training by always being available to help and guide me whenever I needed.

The clinical trials sub-unit, where I spend most of my time, is characterised as a very well-organised unit with 16 years of existence dedicated to clinical research, focused in having a high rate of patient recruitment, while keeping a high standard of quality and patient assistance. This sub-unit is made up of qualified, balanced and efficient professionals, working together so that all procedures of clinical research are performed in compliance with ethical requirements and regulatory guidelines. While the staff is very heterogeneous, with many different backgrounds, they all work toward the same goal, like ensuring GCP's, the well-being of patients and their safety, always with the mind on the protocol requirements.

The time that I spent here allowed me to improve my organization skills, making sure that everything was well organized, in a coherent manner. The daily activities of scheduling appointments, checking the protocol, preparing visits, keeping everything properly signed and dated, making sure that nothing was missed made me focus on the details and understand the purpose of strict organization in clinical research.

With all this effort, I can indicate that the SCs play a very important role in the research unit, being responsible for ensuring that the protocol details are followed, data entry, assisting the monitors, answering calls and managing patients' expectations and apprehensions. Much of the pressure placed on CTs ultimately fall under the shoulders of the SC, due to the fact of being the contact point for all stakeholders. They are instructed to ensure that nothing goes wrong during the trial, and ultimately, to avoid protocol deviations at all costs.

This research site is one of the Portuguese centres with the highest recruitment rate and a low rate of study withdrawals. This express how organized, ambitious and dedicated the staff working in the unit are. Skills like being a scientifically precise and a good communicator are some of the qualities that are shared by all of these professionals. Due to the entire regulatory framework that surrounds this field, it became clear why this qualities are fundamental.

Maybe one of the main difficulties faced by me in this unit as a SC was the coordination of all professionals required to complete the procedures of the patients' visits. Due to the multiple procedures that needed to be performed at each visit, several health professionals are needed, and sometimes bringing everyone together or coming up with a timetable that suits everyone was a true challenge. To overcome this situation, the SCs and I put together the days and hours that each professional would be available in a normal week, in order to try to reach an ideal date. This date would then be discussed with all staff members. Also, when some staff members did not have a fixed schedule, at the end of each visit we tried to program the next ones, in order to leave everything lined up and scheduled. With this experiences, I quickly understood that teamwork is the main ingredient to reach success.

Having a chance to apply the knowledge gained in the bachelor's and master's degree in a real-world context was the main motivation of this internship. The knowledge gained in the last four-years, such as drug legislation, regulatory guidance, laws, ethics documents and anatomy and physiology concepts provided me with a solid background to work in such a regulated and organized environment. Even though that in the first weeks I had some difficulties with dealing the amount of work and responsibilities inherent to the job of SC, I think I was able to gradually adapt naturally. I learned something new every day, and soon I managed to become a productive member of the team. The initial instructions were very important to learn the workflow of the centre, especially some practical things that could not be taught in any theory class, like processing biological samples and measuring vital signs, which were activities unknown for me.

A skill that I think was gained with the time spent as SC was the ability to focus on the bigger picture of a clinical trial while giving proper attention the details, in order to quickly detect any fail in the compliance with the protocol and with GCP. This constant monitoring is important to prevent major deviations that can lead to problems regarding the patients or the sponsor.

One point that I believe that I have improved was how to manage my feelings, though it is still something that I have to improve on. Sometimes it was difficult to maintain the distance between me, as a health professional, and the patient.

Problem solving was another skill that I needed to improve in order to overcome some unpredictable situations. Due to the characteristics of the research group, and the diseases under study (neurological conditions), which lead to us to have more debilitated patients, sometimes some unpredictable situations happened and it was necessary to improvise or change the working method, so that the activities occur as initially planned.

Regarding the trials that I have been involved, they all were very enriching for me, mainly due to its variety of study designs, procedures and different equipment and programs. The variety of designs and settings provided a varied challenge, which required me to internalize a multiplicity of information in a short time. I worked mainly with two diseases: MS and Alzheimer, despite also helping in other trials with different diseases, such as Huntington's disease. Having practical contact with these diseases improved the knowledge that I acquired from my Bachelors in Biomedical Sciences.

From what I observed, this clinical research unit has mainly CTs phase III, IV and OS. Consequently, my experience in here was in phase III and phase IV CTs and OS. It was really interesting to observe the differences between an observational, non-interventional trial in a naturalistic setting, designed to evaluate the real world effectiveness of a drug, with a pre-marketing randomized controlled trial, which have much more inclusion criteria restrictions, usually have more complex protocols and procedures, and much more evaluations during time.

In what concerns my time with the Biostatistics and Methodological Sub-Unit, early on I realized that getting science support must be a top priority. Grants allow researchers to do the job that they might never do otherwise. Some projects are time consuming, and even if their salaries and those of its employees are covered by being attached to a university or a research centre, researchers may not able to buy expensive equipment or cover office expenses values for a year without outside help. Thus, in many situations, grants are desirable or even essential, especially when it's known that the eligibility standards are meet for such awards and a new project or an expansion of an existing project that it's about to start, and the planned costs cannot be covered by the current budget.

I also had the opportunity to improve my communication and selection of important information ability through medical writing activity. With this activity I could complement my experience and expand my knowledge in another areas. I learned to search in databases, how to write a scientific paper and how different are writing' rules according to the journal for which we intend submit the article. It was challenging to do something like that due my difficulty in being objective. However, with this experience I believe I could overcome my difficulties and gain more skills.

Regarding my experience in the UFLVT, I've learned that the raw data must be the only source of information, due to the fact that if someone assumes something based on a person's interpretation of the data, this can lead to errors, misunderstandings, bias, and elimination of evidence, among other deviations to the data source. The work developed in this sub-unit showed me the importance to write all the data and keep all the data sources in order to track cases, documents all fast and precisely and avoid data missing. Moreover, during the daily routine tasks, I quickly realize that attention to detail is crucial in this area, especially when you are working with a lot of information from different sources that trigger different actions and result in different outcomes.

Also, I learned how to perform some of the pharmacovigilance unit daily activities, such as codification of medical terms according to the MedDRA dictionary, the introduction of data in the SVIG, and write causality letters and reports. Additionally, the contact with all the quality documentation (such as operational procedures, data records and the quality manual) made me realize how necessary it is the standardization work through these procedures in order to reduce mistakes, improve the quality and consistent of the work obtained. Finally, the time spent in the UFLVT allowed me to realise the whole process that is required to finalise a spontaneous notification, their importance and their limitations and difficulties.

# 6. Conclusion

Clinical research is a tremendous growth experience for anyone who can work with it. The effort that was done every day, either at the clinical trials sub-unit, where the focus is always the patient, at the production of articles, where the focus is to be as clear as possible, we worked with the hope that we were helping science progress, so that one day, hopefully, terrible chronic diseases like Alzheimer's disease or MS, and many others, will have a cure.

Research requires unconditional commitment, enthusiasm and inspiration. It is important to recognize these efforts, although most of them are invisible to those who benefit from them.

This internship happened within different environments, giving me a wide range of learning opportunities, which allowed me to develop my personal, interpersonal and professional skills, such as responsibility, communication, organisation, problem solving, and autonomy. While the majority of the internship was in CT coordination, I participated on other projects and areas, involving medical writing and pharmacovigilance.

I believe that the internship was a learning experience, where the knowledge obtained from the Master's was constantly refined and improved. I had the opportunity not only to put into practice those concepts learned previously but also develop a great range of professional skills in a short period. During the internship and specially looking back at it, I realize how important my background training was to make easier and smoother the adaptation to the professional environment where I trained.

I have set some objectives in the beginning of this internship, and I feel that I accomplished almost completely all the objectives that I proposed to reach. Working in a teamwork environment was a very gratifying experience, since it make me feel like I fit into a team where everybody sails to the same objective of improving research and providing the best treatments and care to patients.

All the acquired skills and the opportunity to improve and apply the knowledge I already have has motivated me to exceed my expectations, to learn and be involved more on the world of clinical research.

This experience was very rewarding to me because I felt that, directly or indirectly, I was contributing to a positive impact in the life of other people.

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