Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2012

TÂNIA CRISTINA REIS TEIXEIRA

RELATÓRIO DE ESTÁGIO EM MONITORIZAÇÃO DE ESTUDOS NÃO-INTERVENTIVOS

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Relatório de Estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Doutora Maria João de Matos Martins Salgado, Diretora Executiva da Eurotrials, Consultores Científicos e da Professora Doutora Alexandra Isabel Cardador de Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este relatório aos meus pais, Manuel e Margarida, e à minha irmã Isabel por serem o pilar da minha vida.

o júri

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agradecimentos

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palavras-chave

Contract Research Organization, Eurotrials, Estágio, Estudos não-interventivos, Monitorização.

resumo

O presente relatório relata a minha experiência de 9 meses enquanto estagiária da Eurotrials, Consultores Científicos, uma empresa privada especializada em investigação clínica e consultoria científica na área da saúde. O estágio insere-se nas atividades curriculares do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro e teve como principal objetivo promover a "ponte" entre os conhecimentos adquiridos durante o primeiro ano do Mestrado, e o mercado de trabalho, pretendendo servir também como meio de aquisição de novas competências, ao permitir a integração em algumas das atividades desenvolvidas pela Eurotrials. Ao efetuar o estágio no departamento de Epidemiologia & Late Phase research, como monitora, o objetivo foi, também, preparar-me, em específico, para trabalhar na área da monitorização de estudos observacionais/não-interventivos.

Assim, o presente trabalho relata as diversas atividades desenvolvidas numa empresa de prestação de serviços na área da investigação clínica e, especificamente descrever as atividades de monitorização de estudos observacionais/não-interventivos, desenvolvidas durante o estágio.

Este estágio proporcionou uma visão clara e abrangente das atividades desenvolvidas pelas *Contract Research Organizations* (CROs), e dos monitores do departamento de Epidemiologia & Late Phase research em especifico e, permitiu pôr em prática os conhecimentos adquiridos ao longo do Mestrado bem como adquirir novos conhecimentos.

keywords

Contract Research Organization, Eurotrials, Internship, Non-interventional studies, Monitoring.

abstract

This report describes my experience of 9 months as trainee at Eurotrials, Scientific Consultants, a private owned company specialized in clinical research and scientific consultancy in the health area.
This internship occurred during the second year of master's degree programme in Pharmaceutical Medicine at the University of Aveiro and had the objective promoting the "bridge" between the knowledge acquired during the first year of the master's degree and the labour market, and also as a mean to acquire new skills by allowing integration in some of the activities developed by Eurotrials.
Performing the internship in the Epidemiology & Late Phase Research department, as monitor, the goal was also to prepare myself, in particular, to work in the area of monitoring of observational/ non-interventional studies.
Thus, this report proposes to disclose several activities developed in a company which provides services in the field of clinical research and specifically describing the activities of monitoring observational/ non-interventional studies, developed during the internship.
This internship has provided a clear and comprehensive overview of the activities carried out by Contract Research Organizations (CROs) and their monitors and allowed me to put into practice the knowledge acquired during the master's degree and also acquire new knowledge.

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Abbreviations

AB	Administration Board
ACES	*Agrupamentos de Centros de Saúde* – "Health centres Groups" - created under law decree 28/2008 of 22 February
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ARS	*Administração Regional de Saúde* - Local Regional Health Administration.
CEIC	National Ethics Committee for Clinical Research
CES	*Comissões de Ética para a Saúde* - "Health Ethics Committees"- the Committees created under law decree 97/95 of 10 May
CNPD	*Comissão Nacional de Proteção de Dados* - Portuguese Data Protection Authority
CRF	Case Report Form
CRO	Clinical Research Organization
CRA	Clinical Research Associate
CTA	Clinical Trial Assistant
CV	*Curriculum Vitae*
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
GEP	Good Epidemiological Practices
GPP	Good Pharmacoepidemiological Practices
IAPMEI	Institute for the Support of Small and Medium-sized Enterprises
ICH	International Conference of Harmonization
ICH CGP	International Conference of Harmonization (ICH) Good Clinical Practice (GCP)
INFARMED	National Authority of Medicines and Health Products
ISO	International Organization for Standardization
KOLs	Key Opinion Leaders
NHS	National Health Service
PM	Project Manager

PROs	Patient Reported Outcomes
QoL	Quality of Life of patients
RCTs	Randomized Controlled Trials
R&D	Research and Development
SAE	Serious Adverse Event
SDV	Source Data Verification
SMEs	Small and Medium-sized Enterprises
SOP	Standard Operating Procedures
UKAS	United Kingdom Accreditation Service
US	United States
WHO	World Health Organization

1. Introduction

In the scope of the second year of the Master in Pharmaceutical Medicine, I had the opportunity to carry out an internship. This internship carried out from September 2011 to July 2012, in the department of Epidemiology & Late Phase Research, of Eurotrials, Scientific Consultants.

1.1 Objectives

The main objective of the internship in the department of Epidemiology & Late Phase Research, of Eurotrials, Scientific Consultants is to promote the "bridge" between the knowledge acquired during the first year of the Master's degree, and the labour market. By allowing integration of some activities undertaken by Eurotrials, it also intended to serve as a mean to acquire new skills in a specific area (non-interventional studies) and prepare myself to work in this area.

1.2 Structure of internship report

This report is intended to describe the experience acquired and activities performed during the internship of 9 months under the supervision of Dr. Maria João Salgado, Executive Director of Eurotrials, Scientific Consultants, as well as identify the rationale for conducting observational/non interventional studies, characterize the role of the CROs, characterize the host company and describe the activities and experience acquired during the internship. Taking this into account, this report is divided into six chapters, as follows:

- **Chapter 1 – Introduction:** This chapter describes the main goals of the internship and the organization of the present report;

- **Chapter 2 – Overview of observational studies:** This chapter describes the state of the art of pharmaceutical industry and identifies the rationale for conducting observational/non-interventional studies. Observational studies are presented and described, and a comparison is made between clinical trials and observational studies;

- **Chapter 3 – Overview of the host company - Eurotrials, Scientific Consultants:** This chapter identifies some challenges faced, now-a-days, by pharmaceutical industries and the role of CROs. It also describes Eurotrials company. For this, is made a presentation of the company, its organization, the activities performed, as well as its certifications. Similarly, in subchapter 3.3 and 3.3.1, is made a presentation of the Epidemiology & Late Phase Research department (department´s presentation: type of activities performed, organization, among others), and a characterization of the studies developed in this department and also the type of sponsors/ partners involved and with what objectives;

- **Chapter 4 – Description of ongoing studies and activities performed during the internship:** This chapter begins with the identification of the type of studies in which I was involved and with the identification of some differences between them. After this, and throughout this chapter, are also contextualized and described the main activities carried out during the 9 months of internship;

- **Chapters 5 – Discussion:** This chapters aim to give an overview of the internship, especially regarding the experience acquired;

- **Chapter 6 – Conclusion:** In this chapter I present a conclusion about the performed internship.

2. Overview of observational/non-interventional studies

2.1 State of the art

Currently, pharmaceutical industry continues to have a very important role for European competitiveness. In 2011, Europe remained the second largest market for pharmaceutical sales and, the pharmaceutical industry was one of the few sectors to contribute positively to the trade balance of the European Union (EU), with a trade surplus of €48,3 billion (the largest among of the high-tech industries) (1). The pharmaceutical industry also plays a key role in the national economy and is considered a strategic sector for Portugal (2, 3). However, we are witnessing a major shift in society's expectations in relation to medicinal products, particularly regarding the ratio of risk/ benefit and cost/ benefit. The expectation increases due to the recent technological development and ongoing level of various technologies that may result in numerous new diagnostic and therapeutic methods (4). It is known that in the last decade there has been an enormous advance in the basic sciences and technologies as genomics, proteomics, metabolomics, bioinformatics and imaging. Nevertheless, despite the increase of scientific knowledge and the increase of direct investment in Research and Development (R&D) of drugs, the number of new drugs decreased (productivity gap) (5).

In addition to the difficulty of producing drugs that are innovative, development times are extremely long and the failure rates are very high (this is called attrition rate), since the success rate is only about 11% which means that if 100 drugs begin to phase I, only approximately 11 is going to complete the clinical development phase and be approved. This leads to an unsustainable situation of cost of R&D of a new drug have reached values close to €1 billion (see figure 1) (6).

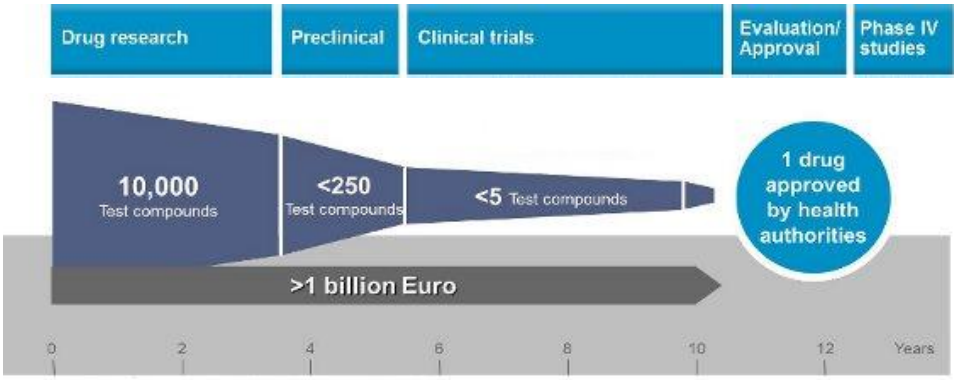

Figure 1: Clinical development phase: long development times and high failure rates (6)

For the current difficulties in developing new drugs can be overcome, it will become essential to implement a new model which adopts new technologies to improve the understanding of the disease, reduce costs and increase R&D productivity. It is also important to start working much more closely with governments, regulatory agencies and medical community, to produce new drugs that patients really need and test them, in humans, as quickly and efficiently as possible. In this sense, the current model of development, with its four distinct phases of clinical testing, will gradually evolve into a process that is more flexible, integrates and more receptive to rapid feedback from patients and providers: The "live-licensing & in-life testing" model (7).

With the "live-licensing & in-life testing" model, companies will perform a series of studies to ensure a full understanding of efficacy and safety profile of the product, before submitting the data to the relevant regulatory agency. Once there is sufficient evidence to show that a medicine works and it is cost-effective in the initial trial population, the regulatory agency will issue a "live license" that will allows the company to market the medicine on a restricted basis (conditional approval) and conduct in-life testing of that medicine. With each incremental increase in evidence of safety, efficacy and value, the regulatory agency will extend the obtained license to cover different and more patients or multiple indications (see figure 2) (7, 8).

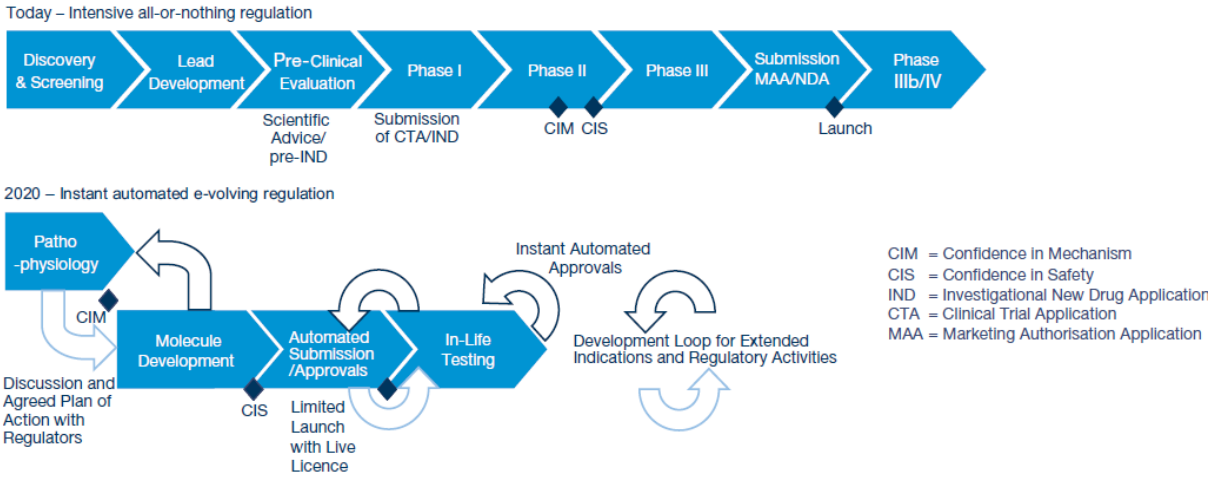

Figure 2: Actual model *versus* "Live-licensing & in-life testing" model (6)

This new model has several advantages (for example allows reducing clinical development costs and aligning the bench and the bedside more closely) but will have the inevitable consequence of the need to continue studying the medicine after their marketing introduction. Therefore, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) will place more emphasis on post-marketing surveillance studies, and all of this will lead to an increase necessity to perform observational/non-interventional studies for obtain evidence that new medicines are safe and effective, in different patients population, and also that are better than others comparable therapies (7, 9).

2.2 Overview of observational/non-interventional studies

In the last half century there have been many medical advances, verified in world population, that enabled the emergence of new medicines, vaccines and other medical tools that contributed to extraordinary gains in terms of health. The effective use of new medicines has led to increased longevity and improved the quality life of patients. The emergence of new medicines also allowed obtaining important social and economic benefits for patients, and even for the economy in general (10).

It is known that the discovery of new medicines is governed by strict principles of organization and planning of the research methodology. The development of new molecule includes, as a first stage, a thorough evaluation by laboratory tests, which permits extrapolation of results in the absence of evidence of potential toxicity problems. There is a phase of exploratory tests (exploratory development) and the first exposure in humans (first in man). The next stage (full development) requires the conduct of clinical trials, which includes the classic phases (phases I to III) essential for the initial approval of the drug by the competent authorities. Clinical trials are the universally accepted method for research (11).

According to the Guideline of Good Clinical Practices E6(R1), a clinical trial is defined as *"Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy".* The terms clinical trial and clinical study are synonymous (12).

In this way, it is easily understood the need of having a very tight regulation and with high complexity of scientific, ethical and legal level. Therefore, between the laws and regulations applied to this area, stand out the followings (13):

- Declaration of Helsinki (2008 version) - definition of ethical principles for medical research involving human subjects (14);
- ICH GCP E6(R1), Good Clinical Practices - an international standard for the conduct and reporting of clinical trials (12);
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 - provides the requirements for the conduct of clinical trials in the EU. The scope is about the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (15);
- Directive 2005/28/EC of 8 April 2005 - established principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products. Concretizes the clinical trials directive (16).

National Law:

- Law no 46/2004 of 19 August - transposition of Directive 2001/20/CE. Approving the legal regime for the conduct of clinical trials with medicinal products for human use (17);
- Law no 67/98 of 26 October - protection of personal data (18);
- Decree-law no 102/2007 of 2 April - transposition of Directive 2005/28/CE. Established the principles and guidelines of good clinical practice in regards to the investigational medicinal products for human use, as well as the special requirements for manufacturing authorization or import of these products (19).

The main objective of the above mentioned legislation is to have common rules in the clinical research area and to ensure that the human dignity and fundamental rights of the participants in the studies are respected.

Clinical trials are highly legislated and provide evidence of efficacy and safety of new drugs in a limited set of patients with particular clinical situations and for limited periods of time, essential for obtaining marketing authorization of these new drugs. However, observational studies are more suitable to detect rare or late adverse effects of treatments and, currently there is a growing need and importance of collecting data in "real life" in order to provide data for the different stakeholders (pharmaceutical industry, health authorities, payers, patients) on the effectiveness and safety of drugs in "real life" as well as the consumption of health care resources associated to the introduction of new therapies (20).

Increasingly, there is recognition of the role played by data about patients' use in normal clinical practice or in settings better reflecting the reality of health care delivery. The collection and use of "real world" data[1] can enable all parties to achieve their objectives and, ultimately, to maximize patients' health gains given the limited National Health Service (NHS) resources (21). Having said this, it becomes necessary to perform another type of studies to obtain more data about the "real life". Thus, in order to bridge the limitations of data obtained by clinical trials (from a limited set of patients with particular clinical situations and for limited periods of time), it is necessary to carry out observational/non-interventional studies, in an environment of normal clinical practice, with a larger, and more diversified, population.

Observational studies are epidemiological/ non-experimental studies that do not involve intervention (22). According to Article 21 of Directive 2001/20/EC, a non-interventional trial is defined as: *"a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data"* (15).

Taking this into account, it is important to note the existence of observational studies conducted with drugs according to the marketing authorization who follow clinical practice, without additional procedures (pharmacoepidemiological studies) and also the existence of observational studies without drugs, such as disease/patients registry studies, genetic characterization of diseases among others.

Another of the aspects that differentiate clinical trials and observational/non-interventional studies is the almost complete lack of regulation of the latter, with except the existence of the Eudralex vol 9A - 2007 legislation for post-authorization safety studies (PASS studies, which aims to identify and/or characterize a safety problem concerning an approved drug) (23). However, there are some guidelines that should be followed when designing, conducting and reporting non-interventional studies, namely:

- Good Epidemiological Practices (GEP) 2007 - guidelines for proper conduct in epidemiologic research. The aim is to provide a set of guidelines for the conduct of high quality epidemiological research and proper collegiate behavior (24);

[1] Real world data has been defined by an International Task Force as data used for clinical, coverage, and payment decision-making that are not collected in conventional randomized controlled trials. Real world data describes what is really happening in everyday normal clinical healthcare practice. This can include data from existing secondary sources and the collection of new data, both retrospectively and prospectively.

- Good Pharmacoepidemiological Practices (GPP) 2007 - intended to propose minimum practices and procedures that should be considered to help ensure quality and integrity of pharmacoepidemiologic research, and to provide adequate documentation of research methods and results (25);
- Volume 9A (Rules Governing Medicinal Products in the European Union) - guidelines on pharmacovigilance for Medicinal Products for Human use. Intended to provide general guidance on the requirements, procedures, roles and activities in this field, for both marketing authorization holders and Competent Authorities of medicinal products for human use; it incorporates international agreements reached within the framework of the International Conference on Harmonization (ICH) (23);
- AHRQ (Registries for Evaluating Patient Outcomes) - intended to support the design, implementation, analysis, interpretation, and quality evaluation of registries created to increase understanding of patient outcomes[2] (26);
- STROBE (Strengthening the reporting of observational studies in epidemiology) Guidelines - to provide guidance on reporting the observational studies results. For this, was developed a checklist of 22 items essentials to improve reporting quality (27).

Nevertheless it is being made an effort on standards creation to perform a better non-interventional pharmacoepidemiological research. An important advance in this sense, was the EMA initiative in establishing the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

The main objective of this network is enable the acess to a robust network of resources for improve risk-benefit monitoring, pharmacoepidemiological research and post-authorization safety surveillance of medicines across Europe, based on principles of transparency and scientific independence (28). As example of ENCePP resources we can have (29):

- ENCePP code of conduct - which objective is to provide a set of rules and principles for the conduct of pharmacoepidemiology and pharmacovigilance studies (30);
- ENCePP checklist for study protocols - intended to promote the quality of studies by stimulating the consideration of important epidemiological principles to design a pharmacoepidemiological or pharmacovigilance study performed in the EU and for writing a study protocol (31);

[2] A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. A registry database is a file (or files) derived from the registry.

- ENCePP guide on methodological standards in pharmacoepidemiology - gives an overview of the internationally acknowledge recommendations with the final objective to assure quality in the studies performed by the European network (32);
- ENCePP database of research resources - an electronic database that comprises two Indices: the Inventory of ENCePP research centres and the registry of EU data sources, and offers information in the available sources of expertise and research experience, in the field of pharmacoepidemiology and pharmacovigilance, across Europe (33).

In the Inventory of ENCePP research centres it is possible to identify that, there are seven Portuguese ENCePP centres registered, which includes Eurotrials.

On the other hand, among European countries, it's also noted that, despite the different requirements regarding the approval by Ethics Committees and different procedures for the informed consent (depending on the study design), most of the countries have legislation regarding protection of personal data. In Portugal, in particular, the deliberation of the National Commission for Data Protection (CNPD), applicable to this type of study, is the CNPD Deliberation No. 227/2007. The applicable CNPD Law is No. 67/98.

In summary, epidemiological or observational/non-interventional studies, unlike clinical trials do not involve active intervention (34). The observational studies are mainly focused in studing the effectiveness (eficacy in the real world), they study a wide and unrestricted population, do not required an intense ICH-GCP compliant monitoring and are less expensive when compared with clinical trials (see table 1).

Table 1: Summary of differences between randomized controlled trials and real world studies (21)

	Randomized Clinical Trials	Real World Studies
Type of Trial	Experimental / interventional	Observational/ non-interventional
Primary focus	Efficacy, safety and quality	Effectiveness
Patient population	Narrow and restricted	Wide and unrestricted
Monitoring	Intense (ICH-GCP compliant)	None / standard clinical practice
Cost	More expensive	Less expensive

Taking all this into account, it is possible to understand the importance of performing clinical trials in order to provide evidence of efficacy and safety of new drugs (in a limited set of patients with particular clinical situations and for limited periods of time), essential for obtaining marketing authorization of these new drugs, and also the importance of performing observational/non-interventional studies in order to provide data for the different stakeholders

(pharmaceutical industry, health authorities, payers, patients) on the effectiveness and safety of drugs in "real life" as well as the consumption of health care resources associated to the introduction of new therapies (see figure 3).

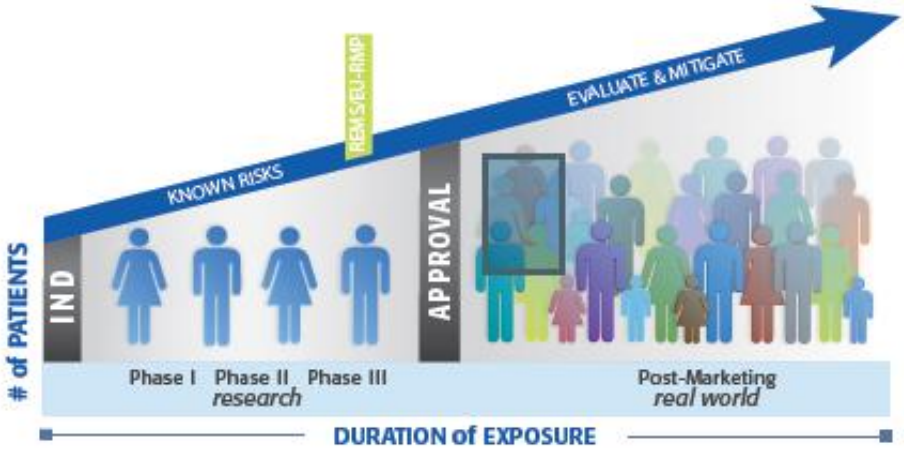

Figure 3: Clinical trials and Late phase studies (35)

Regarding the epidemiological studies the historical context of epidemiology and its contributions to health promotion and disease prevention, justified its recognition as essential in the global strategy for health, for all by the World Health Assembly in May of 1988 (36). Epidemiology is a basic science and clinical medicine, fundamental to characterize health problems, from initial diagnosis to its control, therefore the study target is human population and, according to the Last (1998) definition, the scope of epidemiology is *"the study of distribution and determinants of health conditions or events associated with them, in specific populations and the application of this study to control health problems"* (37). Thus, epidemiology is not only related with death, illness or disability, but also with more positive health states and which means to improve health. So, in recent years the value of information about disease distribution for planning the delivery of health care has become more evident and there is also an increasing interest in studying the effectiveness of the health-care system and/or of different treatments (38).

In what concerns to clinical epidemiology, the methods may be applied to answer the clinical questions, useful in patient care, namely: etiology, diagnosis, prognosis, treatment, prevention, evaluation of health care services and analysis of risks and benefits, and for this, there can be used different designs and types of studies (36).

However this situation should be well analysed because the choice of an appropriate study design is a crucial factor in conducting observational/epidemiological studies. Still, we can say that design

is no better or worse than the other, it may be more or less appropriate depending on the study question and the general circumstances involved (39, 40).

In the following figure it is possible to observe different types of study designs and associated features:

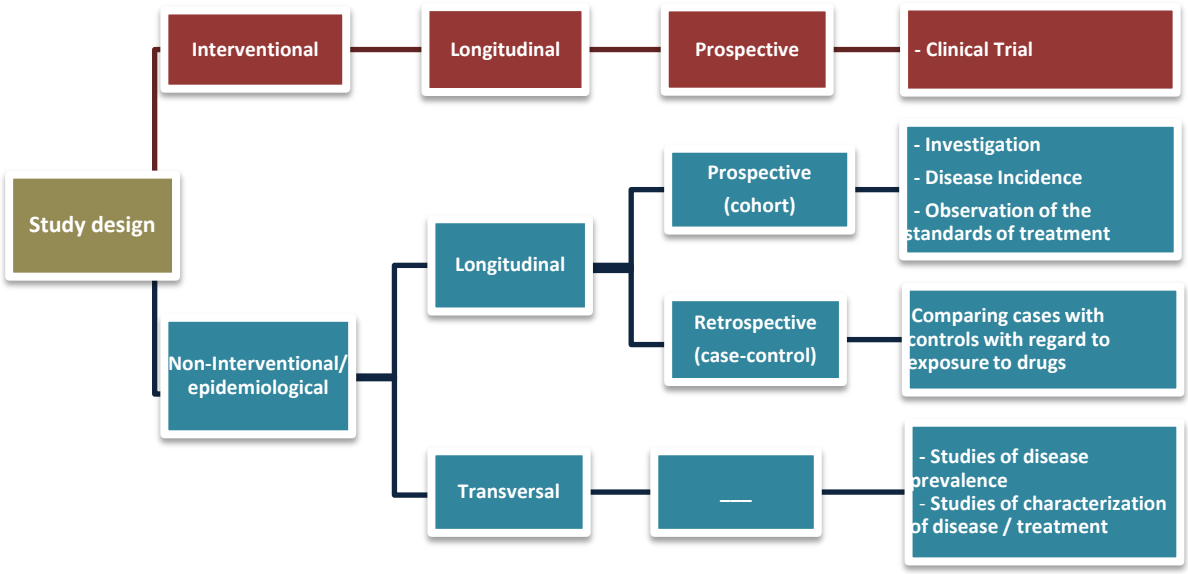

Figure 4: Epidemiological studies: designs and characteristics (41)

Regarding to the designs it is important to highlight that the studies can be carried out by retrospective or prospective data collection. A prospective study is an observational study, often longitudinal in nature, for which the consequential outcomes of interest occur after study commencement. On the other hand, a retrospective observational study employs existing secondary data sources in which both exposure and outcomes have already occurred (42). So, for choosing the appropriate methodology, there are some factors to consider (see table 2):

Table 2: Prospective and retrospective designs - applications, vantages and limitations (21)

	Prospective	Retrospective
Scope of dataset	Can include data not routinely recorded e.g. formal disease rating scales, Patient Reported Outcomes Data reflects current treatment	Can only include routinely recorded data Need to balance need for current data vs. eligibility period need to obtain enough patients vs. number of sites
Timelines	Depend on rate of presentation of suitable patients	Predictable, short data collection period
Patient consent	Easy to seek as patient present to clinic	Can be more difficult to obtain

As a example of the studies with these designs, we can have, not only but also the followings (21):

- **Retrospective design:**
  - Retrospective chart review;
  - Primary care database study;
  - Secondary care database study;
  - Case-control study;
  - Cohort study.

- **Prospective design:**
  - Cohort study;
  - Prospective outcomes study;
  - National registry;
  - Patient reported outcomes[3] study (21, 43);
  - Post marketing surveillance/safety study.

Among the epidemiological/ observational studies, stand out the cohort studies and case-control studies. They have some similarity with experimental studies, namely two groups, one of which is the control group. However, they are not experimental since there do not have randomizations or manipulation of exposure.

[3] Patient-Reported Outcomes (PROs) are reports coming directly from patients about how they feel or function in relation to a health condition and its therapy without interpretation by healthcare professionals or anyone else. These survey instruments provide an important and highly relevant way of assessing the effects of treatment, which are complementary to conventional clinical endpoints.

In cohort studies are formed groups of exposed and unexposed and they are followed for some time in order to determine the occurrence of the disease in focus and the relation with the exposure of interest (see figure 5). These studies can be prospective or retrospective (40, 44).

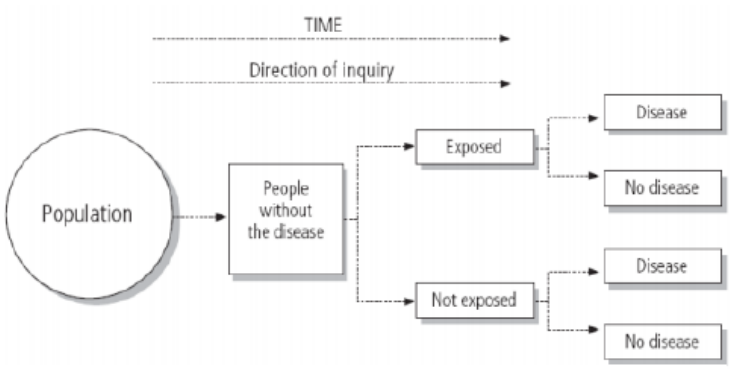

Figure 5: Cohort Studies (37)

On the other hand, case-control studies compares prevalence of risk factors in a sample of individuals with the disease (cases) and the prevalence in a sample of individuals without the disease (controls) and, after, looks to the past (retrospective design) to identify differences that may explain the reason for cases developing the disease cases and controls did not (see figure 6) (40, 45).

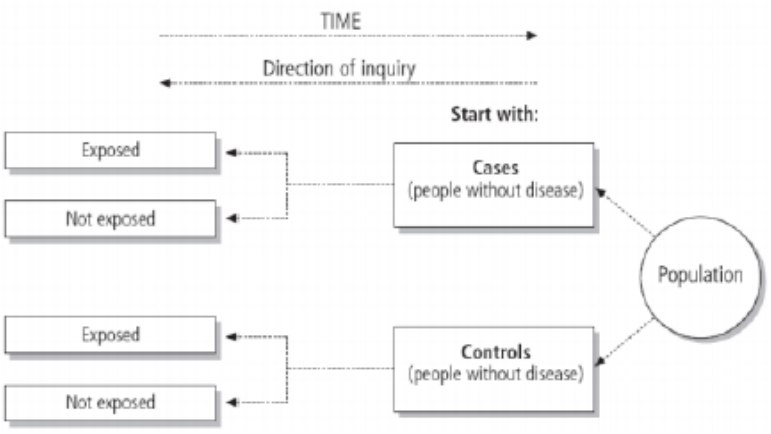

Figure 6: Case-control study design (37)

Moreover, there are also cross-selection studies, also known as prevalence studies, which determine the distribution of health states and their determinants, in a population at a particular moment in time (see figure 7). In this studies, the measurements of exposure and effect are made at the same time (37, 44).

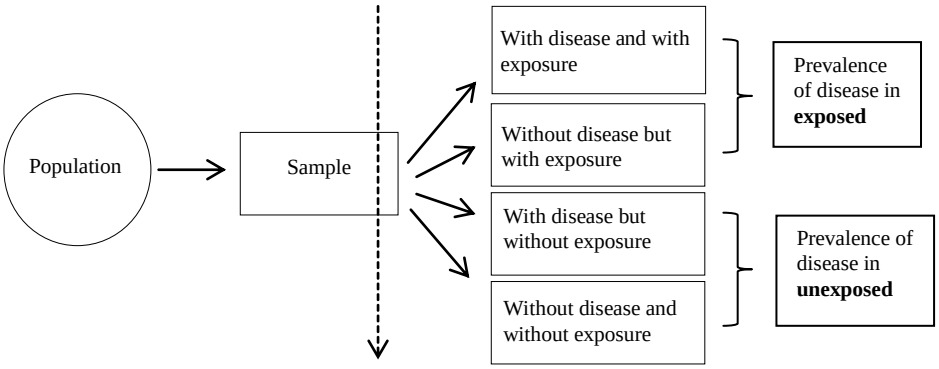

Figure 7: Cross-selection study design (adapted from reference (39))

3. Overview of the host company - Eurotrials, Scientific Consultants

3.1 Overview of Contract Research Organizations

Throughout the history of pharmaceutical industry, big companies have always tried to carry out all stages of R&D internally, with infrastructure and its own staff (46). However, the increasing pressure on the global pharmaceutical industry costs, due to declining productivity of R&D, longer R&D timelines and increased costs to develop new medicines and for legislative requirements, has led to the increase of outsourcing of some stages of the process of R&D (46).

The research or study is then possible to be performed not only through internal resources (in-source), as well as through to external resources (outsource), that occurs when pharmaceutical companies contract third parties to conduct their studies (47). So, the outsourcing can be contracted locally or at a global level. Regarding advantages and disadvantages of this, it is possible to say that internal resources have as advantages the relationship that is established between researchers and Key Opinion Leaders (KOLs), competitive intelligence, business culture, higher availability, the first contact to new therapeutic areas and synergies with other structures of the company. However, on the other hand, these resources have also disadvantages, such as, the need for greater investment in education and training, and the existence of a heavier structure (48). Thus, the increasing cost pressure on the global pharmaceutical industry and the increasing pressure to bring more new drugs to the market while at the same time they have to cut their R&D budgets, has led, increasingly, the companies to search for outsourcing their R&D to Contract Research Organizations (CROs) (see figure 8) (47).

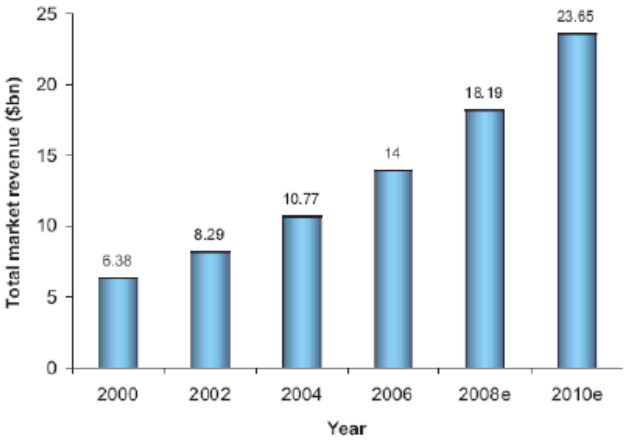

Figure 8: Estimated CRO total market revenues, 2000-2010 (49)

The CROs offers many services that the pharmaceutical industry do not have or are not willing to maintain in its organizational structure, namely:

- Medical writing;
- Regulatory support;
- Centre/Investigator selection and qualification;
- Study management and monitoring;
- Pharmacovigilance;
- Drug management;
- Data processing;
- Data analysis (biostatistics).

The CROs services can help to alleviate the constraints verified at pharmaceutical industry level and can increase R&D effectiveness and at lower costs (48). In the same way, the CROs services can representing a greater structural flexibility, greater sense of urgency and also the existence of immediate resources that can fill gaps in the areas of competence (50). However, despite sponsor can outsource their R&D to the CRO, during the course of the study or before the start of it, and may transfer some or all of its obligations and functions related to the study, it should be noted that the last responsibility for the quality and integrity of the data will be of the sponsor.

CROs have the capability to design, implement, conduct, collect and process data from clinical trials and observational/non-interventional studies, leaving the pharmaceutical industry to define the role of development strategy (clinical trials) and maintenance lifecycle of their products (observational/non-interventional studies).

In Portugal, in accordance with the world situation, there is a growing pressure on the pharmaceutical industry in order to ensure that the cost and the time to market of new products are reduced. This pressure leads to that, in Portugal, there is also an increase of the search for the CROs services, opting for lighter and more flexible structures (48). There are several such organizations but one that stand out is the Eurotrials, Scientific Consultants, a CRO specializing in clinical research and scientific advice in health sciences.

3.2 Overview of the host company - Eurotrials, Scientific Consultants

My internship took place at Eurotrials, Scientific Consultants, a privately owned company founded in Lisbon in 1995 by members of academia, medical community and pharmaceutical

industry, that operates in Europe and Latin America (Brazil, Argentina and, more recently, in Chile) (51).

Eurotrials have expertise on clinical research and scientific consulting in health sciences and is committed to provide quality and efficiency services at international level, in the optimization of existing research centres and in the development of research centres of high potential, training and motivating new human resources in clinical research and in establishing strategic partnerships which includes pharmaceutical industry, healthcare institutes and medical societies and associations (see table 3) (52):

Table 3: Eurotrials partners

Eurotrials partners	
Pharmaceutical industry	Consultancy firms
Biotechnology companies	Institutions: health and others
Medical devices and diagnostics companies	Health regulatory authorities
Hospitals and clinical research centres	Foundations
Research sites networks	Corporate technology centres and business associations
Medical societies and associations	IT companies
Research institutes	Financial groups
Others CROs	Food sector companies
Healthcare professionals	Medical hydrology companies
Patient associations	Cosmetic companies

Eurotrials is proposed to undertake the production of science and technology able to compete nationally and internationally and is recognized and certified by different entities:

- **ISO certification** - ISO 9001 quality certification from Lloyd\'s Register Quality Assurance with UKAS (UK Accreditation Service). After that, in 2002, Eurotrials had another step in the consolidation and guarantee of this work philosophy, with a transition to ISO 9001:2000. In 2009, Eurotrials accomplished the transition of the certification to ISO 9001:2008 (53).
- **"*Rede PME Inovação COTEC*" -** an initiative designed to promote public recognition of a group of Small and Medium-sized Enterprises (SMEs) whose innovative attitude and activities make them an example of creation of value for the country (53).

- **Leading SME -** that recognized Eurotrials as a leading SME because was considered by the organization as a driving force in the national economy, due to the quality of their performance and their risk profile (53).

Eurotrials is qualified to participate in all the steps of any clinical, translational or epidemiological research project, from the initial research question to the availability final results or final publication. So, in order to be able to perform its services and activities, Eurotrials is organized in the following departments, which communicate and interact with each other (see figure 9) (54):

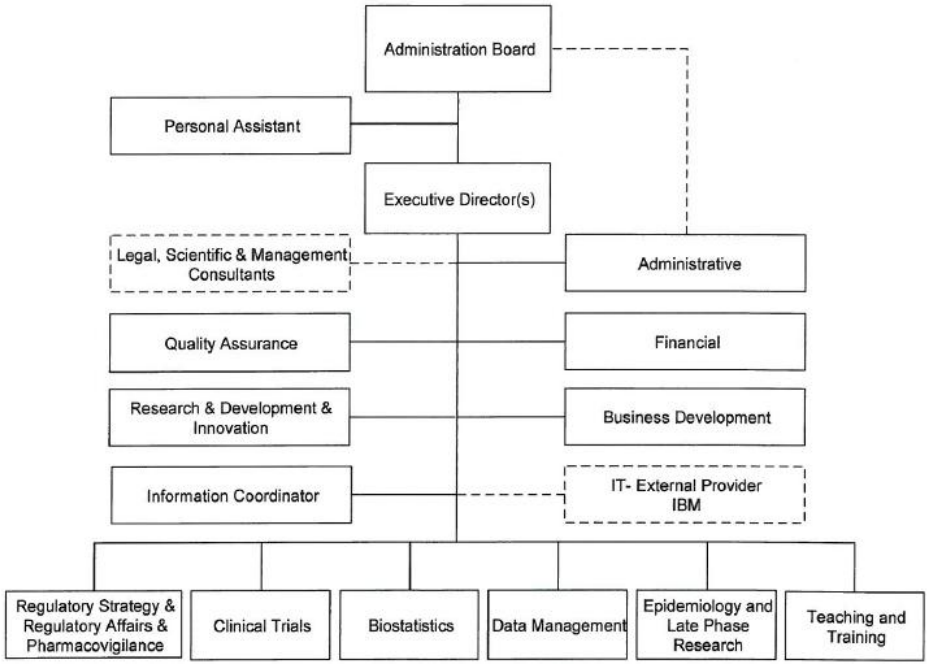

Figure 9: Eurotrials Portugal organizational chart (54)

3.3 Overview of Epidemiology & Late Phase Research department

Epidemiological studies and Late Phase Research studies were initially conducted by the clinical trials department, the largest department and the first to be created in the Eurotrials however, due to the growth of this type of studies, was created, in 2000, a independent department to carry out the activities related to non-interventional studies the Epidemiology & Late Phase Research department.

Although this department is still quite small when compared with the clinical trials department, it has already, a diversified constitution, that can be justified by the great diversity of

services performed that can go from the study design, conception of the project (protocol development, as well as patient information and informed consent forms, case report form, etc.) until the publication of scientific results. In this way, the employees of this department are involved in different type of activities, in close collaboration with the other departments from the company, such as:

- Conception and methodological design of studies;
- Development of study protocol, as well as other documents such as patient information and informed consent forms, case report forms, questionnaires, diaries, specific forms of study, and others (as applicable);
- Study submission to health authorities (CNPD, Ethics Committees, Administration Boards, among others, depending on the study), and subsequent interaction with health authorities;
- Centralized project management;
- Development of tools for managing the studies conduction;
- Studies conduction (initiation visits, training sessions, monitoring visits, quality control visits, close out visits, among others);
- Implementation of in-house monitoring activities;
- Contact and support to study investigators or other elements involved;
- Training of investigators/ inquirers/ sponsor teams;
- Surveys execution (street/phone);
- Bibliographic searches;
- Preparation of multimedia presentations;
- Preparation of final report/ scientific articles/ posters.

There are different goals for conducting non-interventional studies, but the majority are related to (55):

- Generation of clinical effectiveness data;
- Support & strengthen the product safety profile;
- Provide “real-world” clinical and economic outcomes;
- Support the development of “best-practice” guidelines, and standards of care;
- Create value for new therapies;
- Support the strategy for hospital access;
- Use objective data to drive product lifecycle planning;
- Maximize communication opportunities with key customers;

- Promote disease awareness;
- Collect diseases prevalence and incidence data;
- Knowledge about the clinical practice;
- Gather information on the management of diseases and use of medication;
- Knowledge of the burden/ impact of disease.

Currently, the Epidemiology & Late Phase Research department relies with the collaboration of 8 persons, including a head of the department, a project manager, a senior monitor (also called as Clinical Research Associate, or CRA), four monitors/CRAs, and a Clinical Trials Assistant (also called as CTA) which gives administrative support to CRAs, (see figure 10 where is represented, schematically, the organization of department).

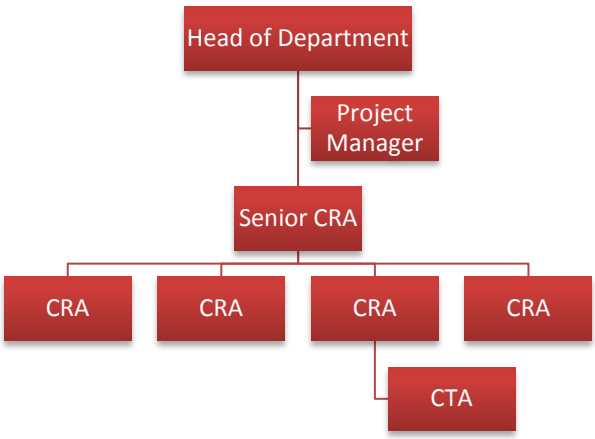

Figure 10: Epidemiology & Late Phase Research department organogram

Eurotrials develops and conducts different type of studies and the majorities are the Community Based studies, followed by Clinical Practice Characterization studies and Pharmacoepidemiological studies (see figure 11).

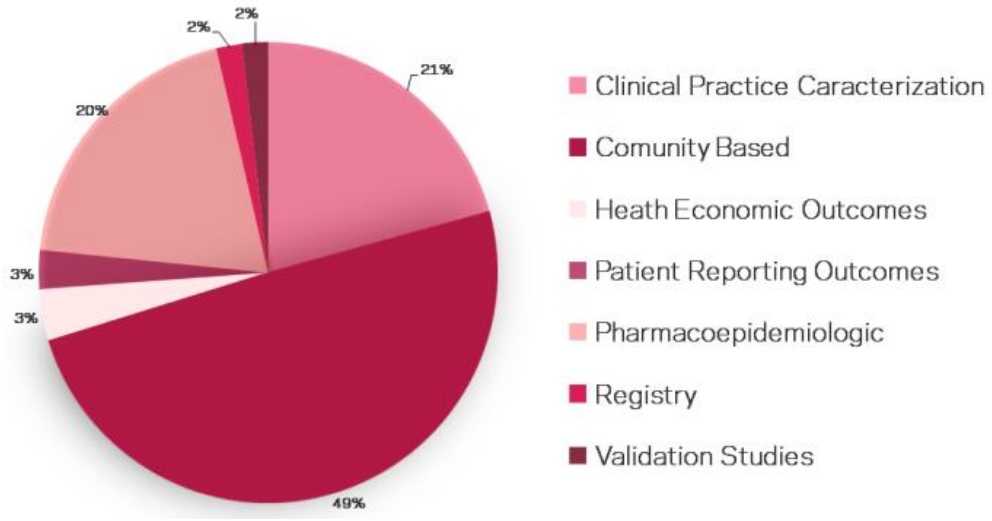

Figure 11: Type of studies developed by Epidemiology & Late Phase Research department (56)

However, in the last years the Health Economic Outcomes studies are growing mainly due to the health authorities and payers request of evidence of the clinical, economic and humanistic outcomes associated with the market drugs.

These studies can take place in some different kinds of institutions, such as: public and private hospitals/ clinics, primary healthcare centres, other health institutions (for example, medical private offices). Nevertheless, it is important to describe what are the main objectives intended to be achieved with these studies, as well as the type of partners of Eurotrials/ the main type of sponsors.

3.3.1 Characterization of the type of studies conducted and the main partners involved

In the Epidemiology & Late Phase Research department are carried out basically epidemiological studies and Late Phase studies, with differents partners/sponsors (see figure 12).

Figure 12: Type of studies and main partners of Epidemiology & Late Phase Research department (55)

The epidemiological studies, as mentioned above, are fundamental to characterize health problems, from initial diagnosis to their control. In this sense, and due to the lack of epidemiological information on a national level for some diseases, it is essential and appropriate the implementation of studies that estimate the incidence[4] of diseases in the Portuguese population and that characterize other aspects relating to their epidemiology, diagnosis and treatment. So, at Eurotrials, this kind of studies are often performed in this department and the sponsors are, usually, primarily the medical scientific societies, medical community, patients organizations, government agencies, regulatory agency with diverse goals such as: to know the prevalence[5] and incidence of diseases, characterize specific populations, characterize the clinical practice for certain pathologies and measure and evaluate the Public Health measures (37, 57, 58).

On the other hand, in the Epidemiology & Late Phase Research department of Eurotrials are also developed Late Phase studies.

Late Phase studies are a major driving force behind the development of (new) medicines. They can target particular therapeutic areas or populations where relevant clinical data are required to ascertain the effectiveness, safety, acceptability, utilization patterns and cost-

[4] The incidence of a disease is the rate at which new cases occur in a population during a specified period.
[5] The prevalence of a disease is the proportion of a population that is affected by the disease at a specific time.

effectiveness of a product. The existence/availability of epidemiological and post-commercialization studies data are crucial in validating scientific therapeutic, economic and healthcare policy solutions (55). Therefore, these studies are mostly sponsored by the pharmaceutical industry and/or by regulatory agencies and they are very important, in particular, for completing the information obtained in clinical trials, in the previous phases, after obtaining marketing authorization, in order to allow data collection in a "real population". Thus, these studies contribute to the main objective of safety monitoring in a real clinical setting in a large population, they also contribute to assess whether the drug brings, or not, an additional burden to the health care system, in terms of resource utilization and also if it improves the patients quality of life.

In this way, these kind of studies are particularly important, for example, for the following cases:

- To study the clinical "outcomes" in a diversified population, that reflect clinical practice - effectiveness studies;
- To make comparison between several alternative interventions in the "real" population;
- To study the compliance and the Quality of Life of patients (QoL) in a real environment;
- To Collect data usage (data about the consumption of resources in a pathology for assignment of costs and economic evaluations - pharmacoeconomic studies) (59);
- To obtain information on how a product and/or therapeutic strategy is used in clinical practice – characterization of clinical practice;
- To study special populations that are not subjected to clinical trials (eg, pregnant women, children);
- To answer the need and obligation to collect safety data for new drugs after the placing on the market - PASS studies.

Here it should be noted the last point, relating to the need and obligation to collect safety data on new drugs because, in fact, such studies may be required by regulatory authorities when there are a “conditional” drug approval, having as a main objectives the identification of security aspects that may not yet be known, the investigation of the risks already flagged and potential new risks, in order to assess the possible causal associations; confirmation of the safety profile of the drug in "real conditions" and the quantification of unknown, and know, adverse reactions and finally the identification of possible risk factors for certain adverse reactions (60). Indeed

according to the Directive 2010/84/EU, a post-authorization safety study is *"any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures"* (61).

Thus, when we think about potential partners/sponsors of the Late Phase studies, we may have the regulatory authorities, the pharmaceutical industry, and even the governmental entities, the medical community and the patients associations (see table 4).

Table 4: Type of partners/sponsors of Late Phase studies and objectives (62)

Types of sponsors/ partners	Objectives
Regulatory authorities	To collect of safety data after MA To study the effectiveness and resource consumption To compare the cost-benefit of therapeutic alternatives to market entry decision and to the reimbursement process To study populations that are not included on the clinical trials (special populations)
Pharmaceutical industry	To obtain information of the use of a product and/or the therapeutic strategy in clinical practice To study the clinical outcomes in a diverse population that reflect clinical practice To study/characterize patients subgroups that respond differently to a given therapy To study the compliance and the QoL in a real environment
Government entities/medical community/ patient associations	To know the prevalence and incidence of diseases To characterize specific populations To characterize the clinical practice for certain pathologies (e.g. therapeutic strategies used, degree of disease control, among others) To study the impact of the disease on the society

4. Ongoing studies and developed activities

During the 9 months of internship as CRA trainee of Epidemiology & Late Phase Research department, I had the opportunity to participate on a wide variety of studies with different regulatory requirements (see Appendix B - Main studies ongoing during the internship). Since the different studies are performed in different type of sites (primary care, secondary care, private medical offices), I had the oportunity to learn about different requirements for the regulatory submissions for the different kind of sites. Throughout this chapter, I will contextualize some of the activities performed and describe them. However, I will start by refer some of the types of sites in which the Epidemiology & Late Phase Research department has ongoing studies and some differences in conducting studies in different kind of “places” (in open streets, medical private offices, private clinics, primary healthcare centres and in secundary healthcare centres [hospitals]).

4.1 Type of sites of ongoing studies

4.1.1 Ongoing surveys (population surveys)

One of population survey study in which I was involved was an epidemiological study, observational, cross-sectional (see study No. 15 of Appendix B - Main studies ongoing during the internship) whose collection of information was made in domiciles, through the direct and personal approach made by inquirers, by applying a questionnaire/survey to a population sample that was stratified by sex and age group to be a representative sample of the portuguese population.

The data collected in this study was totally anonymous, with no data that could identify directly or indirectly the study participants. For this reason, and since the study was totally anonimous, no personnel data was collected, so there was no necessity to obtain the CNPD approval.

Also no specific regulatory approval was necessary for the study conduction, since these kind of surveys are applied/filled in participants' domiciles. This kind of studies have a fast implementation and conduction even when large number of questionnaires have to be obtained, because there is no need to wait for any regulatory approval to implement and conduct the study.

Regarding the activities performed in the conduction of this study, I had the opportunity to develop some tasks namely the contacts with the inquirers, the collection, review, tracking, and

shipment of the questionnaires to Eurotrials Data Management department of the completed obtained questionnaires and the updating and maintenance of the study files. So, this study allowed me to acquire and develop other skills, such as understand the dynamics of managing and planning the activities of the inquirers and the importance of understanding how the study is progressing in order to better plan the next steps, differents those that will be mentioned in the hospital based studies.

Another survey study in what I was also actively involved, was a study that had the objective of understanding the portuguese reality concerning the screening, referral and selection of antiviral therapy to the patients with chronic hepatitis B (see study No. 14 of Appendix B - Main studies ongoing during the internship). This study was conducted through the application of a survey/questionnaire to a sample of physicians with different specialities. This study, was also quickly implemented, since there was no individual patient data collection, the study was based in the physicians responses to a specific questionnaire, so it was not necessary to obtain any regulatory approval for the study conduction in Portugal. Regarding the activities performed, they were essentially concerning the invitation to several selected physicians (either by email or by phone), the application of the questionnaire by email or phone, giving the necessary support for answering questions and finally the creation of strategies for attracting more physicians to participate in the survey. I also had the opportunity to register the questionnaire answers into a specific database and collaborate in the analysis of the responses.

4.1.2 Ongoing studies in medical private offices

During the internship period, I was mainly integrated in the studies taking place in hospitals. Still, although I had not accompanied the submission phase of some existing studies that took place in medical private offices (see studies No. 5 and 9 of Appendix B - Main studies ongoing during the internship), I executed some in-house monitoring activities (including revision of Case Report Forms [CRFs] to verify the patients eligibility and the, subsequent emission of queries resulting from the revision/verification of CRFs). I also had the opportunity to help in the preparation of some monitoring visits.

Comparing the studies that are conducted in private medical offices with the studies that are conducted in hospitals (public or private), I could learn that, after activation of the sites, the studies are essentially developed in the same way. However, the submission phase is different, since in the medical private offices, there is no Ethics Committee (EC) and/or Administration Board (AB) to submit the study, so it was possible to understand that, in these kind of sites, the studies are more quickly implemented when compared with hospitals that have an local EC/AB, where the study as to be submited for approval.

4.1.3 Ongoing studies in primary healthcare centres

Additionally, I also was involved in some activities of an studies conducted in primary healthcare centers (see studies No. 7, 8 and 12 of Appendix B - Main studies ongoing during the internship). During this study I performed contacts with the local Health Regional Administration (ARS) to obtain information concerning the study submission and I also had the opportunity to participate with the responsible monitor in a quality control visit done to one of the investigational sites.

This study, allowed me to acquire additional knowledge that until now was not possible. I could see that, unlike the private clinics and hospitals, here there is an organization of the primary healthcare centers, by region. In other words, while in the studies that claim to be developed in a hospital environment, the submission is made to the specific hospital, in the case of primary healthcare centers, although generally it is necessary to obtain a authorization from the health care center coordinator to authorize the execution of the study, the study must always be submited and evaluated by the local ARS (ARS North, Centre, Lisbon and Tagus Valley, Alentejo and Algarve, whichever is applicable) depending on the region where the study will take place.

After obtaining the approval of correspondent local ARS, the study may occur in any primary healthcare center in that region (excepting cases where the coordinator of the unit do not authorize and cases where the respective Health Centers Group [ACES] to which the unit belongs, have something to object). However, it was possible to verify that, despite the existence of an EC and a AB, such as in hospitals, the time of approval of the study by ARS may be longer than in hospitals.

Regarding the quality control visit performed, I also had the opportunity to observe that, in that specific site (but similar to what may happen in other primary healthcare centers), the patient clinical file was in paper and also in a electronic format. This situation represented a bottleneck in performing monitoring/quality control activities because the access to the complete patient clinical information becomes more complicated.

4.1.4 Ongoing studies in hospitals (public or private)

As already mentioned, during the 9 months of internship, I was mainly integrated into the ongoing studies in hospitals (see studies No. 1, 2, 3, 4, 6 and 11 of Appendix B - Main studies ongoing during the internship). Unlike described for ongoing studies in private offices, here I could follow the early stage of some studies in hospitals so, I could have a realistic view regarding the procedures for study submissions to the hospitals, as well as to the deadlines for evaluation and approval of each site and even the differences from site to site. Concerning the studies that I was integrated, it should be noted that I participated in some activities in international studies,

however I was mainly involved in national studies, especially in two studies, in neurology area and VIH area, where I developed the main activities that will be described further on this internship report.

4.2 Developed activities during the internship

4.2.1 Confidentiality agreement

Before the beginning of any kind of activity, any new collaborator of the Eurotrials starts by signing a confidentiality agreement. This process has a particular importance in the organizations concerned (CROs) because they work with different sponsors and have access to confidencial information that must be safeguarded. After signing the confidentiality agreement, the new collaborator will begin to have access to information and is then able to start a new phase: the training program.

4.2.2 New employee training program

This training program has a theoretical and practical approach and has been designed in order to train the new collaborator in the activities that he will execute in the future, however the training program also includes the reading of documents that are transversal to all of different departments. In addition to the general training it should be noted that the training program also includes a specific training related to projects/studies in which the collaborator will participate, and these training should be performed throughout the collaborators career path (whenever applicable).

4.2.2.1 General training program

The general training program which is carried out by a new collaborator of Eurotrials, presupposes the reading of essential documents, necessary to perform the activity, such as:

- Standard Operations Procedures (SOPs) of the company (including SOPs in which the training is required by all colaborators and the SOPs that are only mandatory for some collaborators depending of the main activity performed/ department and position. An example is the reading of SOP related to site initiation visit that is not mandatory for

the Biostatistics department collaborators, but the read of staff training SOP is mandatory for everyone);

- Colaborator's manual (which seeks to create the best conditions for the integration of new colaborator to identify themselves, as soon as possible, with the company's culture and be active members of them);

- Other reference documents (GPP, GEP, Declaration of Helsinki, ICH-GCP, local legislation, among others) listed in the matrix of training made available to each colaborator.

4.2.2.2 Training program in specific projects

In addition to the general training in the activities to be performed, it is also essential that the new colaborator receives a training in the project in which he/she will participate. This kind of training includes reading of documentation inherent to the study such as: study protocol, case report form, patient information and informed consent form, therapeutic area, among others. The collaborator can also perform a specific, additional training, provided by the sponsor of the study.

It should however be noted that, although the training programs are critical at the beginning of the activities of the new colaborator, there remains a concern of all colaborators in order to perform new trainings or upgrade existing ones. So, for this the company has an annual training plan developed in order to fill the potential training gaps and this plan is updated frequently in order to meet the needs. There are, some trainings provided every year, regardless that the colaborator already have done it in previous years, such as pharmacovigilance and ICH-GCP training.

During the 9 months of internship, as a collaborator of Eurotrials, in addition to the initial training, I had the oportunity to perform another type of trainings that served as a source of professional enrichment, such as Eurotrials trainings in declaration of Helsinki, introduction to epidemiological research, Law No. 46/2004 clinical trial with the medicines for human use, time management, epilepsy, risk management, data protection legislation and handling of patient data, clinical analysis, excel, among others. In adition, I also performed, autonomously, several specific training for the projects that I was involved and I also performed in the some trainings provided directly by some sponsors of the studies in which I was involved.

4.3 Project specific activities

In this sub-chapter, it will be described the projects specific activities that should be performed in order to properly implement and conduct the observational/non-interventional studies. The projects specific activities includes, in a first stage, the correct planning of study activities, through a investigational site selection and also selection/invitation of the study team, followed by qualification visits and study submissions to health authorities (CNPD and to investigational sites, if applicable). After final approval being obtained from the respective authorities, the next main activity includes preparation of the study initiation and its implementation through the realization of a site visit in order to initiate the study. During the study conduction, regular contacts with investigational teams and monitoring/quality control visits should be done, and at end phase, a last visit to the investigational site will be performed (close-out visit).

4.3.1 Planning and initiation of activities

Before the beginning of any study it is necessary to go first through various stages including the first contact with the future site and research team, collecting documents for study submission to the different entities, accompany the process of obtaining all the necessary approvals, the communication with the differents stakeholders and the preparation of the official initiation of the study. All these stages are of great importance to the continuation of the study and will be addressed below, however the stages described are not mandatory to occur with the same order that here is described.

4.3.2 Site selection and investigational team selection

One of the initial steps of the study involves the identification and selection of possible sites for the implementation of the Epidemiological and/or Late Phase Research study (investigational sites) and the investigational team. This is a very important activity because the success of a study also depends, mainly, on a correct selection of investigators. The identification of possible investigators should be made considering different sources of information available by the time of selection, namely based on sponsor's suggestion, based on available information about the experience of the potential investigator, investigator's interest regarding the project and his/her availability for its conduction/participation.

On the other hand, the initial selection of the participating investigational sites may be performed by sponsor or by the PM/ CRA of the study, if applicable, taking into account the evaluation of important parameters such as: local EC/AB time for approval (when applicable); site logistic conditions; availability and human resources; GPP, GEP and/or GCP compliance and available population for the study / predicted recruitment rate. However, it is also important to note that depending on the type of studies to be implemented, some requirements can be different, for example, for an Epidemiological and/or Late Phase Research study where the data is obtained by phone or by direct request interview to passer-by people in the open street or houses, the main selection objective may be only select representative regions of the country.

This selection and identification is a responsibility of the sponsor or of the sponsor representatives, so the study PM or study CRA can be responsible for identifying and selecting the investigators that will participate, if agreed with the sponsor. However, in most studies in which I was involved, the selection was always performed by the sponsor and then the monitoring team had the responsability of contacting potential investigators, again, to confirm their interest, availability and conditions to participate in the study. For this, the study documentation was sent to the sites only after the confidentiality agreement had been signed by the study team, in which they assumed the commitment to confidentiality regarding to the study information that they would have access. Having said that, not only with a view to better inform potential researchers but also in order to properly plan the subsequent phases, it is important to present documentation and training in the main study, which usually includes the:

- Study Protocol (or synopsis);
- Case Report Form.

The CRA/monitoring team should then have training in these documents (or other, if applicable, such as scales, pharmacovigilance forms, among others) so that it can transmit crucial information and clarify any questions that may arise.

4.3.3 Qualification visit

Even at the stage of selection of the sites and investigational teams, but after the initial selection of the participating sites, qualification visits/calls can be performed to the investigational sites in order to better assess the existence of conditions for the development of the study and evaluate some issues such as: the site's facilities, namely human resources, logistic issues (for example, the existence of computer equipment in case study provides an electronic

CRF), the average time to approval of the applicable entities and recruitment potential of the site for implementing the study.

At the Epidemiology & Late Phase Research department, the qualifications visits are not very common, so during the internship, I had no opportunity to participate in this type of visits, however all of these points are addressed and discussed remotely (by phone) prior to the potential submission of the study to the site.

4.3.4 Submission to CNPD and Local EC/AB

Although, most of the times, the investigational sites and investigational teams are already chosen by the sponsor, the study cannot start prior to obtaining approval by Local EC/AB. In this way, it is essential that the documentation of the study (protocol, patient information and informed consent form, CRF and other documents in which there might be data collection, such as scales, questionnaires, diaries and pharmacovigilance forms) are submitted for review and approval of such entities.

4.3.4.1 Submission to the National Authority for Data Protection

Regarding the submission of non-interventional studies, it is not necessary to submit these for evaluation and approval by the National Ethics Committee for Clinical Research (CEIC), whose mission is to ensure the protection of the rights, safety and welfare of partcipantes in clinical trials, by issuing an ethical opinion about research protocols that are submitted (63) and, by the National Authority of Medicines and Health Products (INFARMED), whose main mission is to ensure the quality, safety and efficacy of medicines and health products, ensuring the highest standards of public health and the consumer protection (64). However, such as in clinical trials, generally, it is necessary that all non-interventional studies are submitted to the Portuguese Data Protection Authority (CNPD – *Comissão Nacional de Proteção de Dados*) since, in most studies, it is necessary to collect identificable data of patients[6]) (18). Here it should be noted that, although being more common, first to perform the CNPD submission, this can also be done in parallel with the submission to the investigational site, however the study cannot start prior to obtaining the approval of the CNPD.

Regarding to CNPD submissions and once I followed the initial activities of some studies, I had the opportunity to perform and/or collaborate on some electronic submissions to the CNPD,

[6] It is considered identifiable the person who can be identified directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

and also to follow-up the process until final approval and also notify the CNPD about the occurrence of minor amendments to the study documentation. So, I could learn that the notification procedure starts with the preparation of a request for authorization to CNPD. The application is submitted totaly electronically, through the completion of a online form, available on CNPD website. This request must include some information required by CNPD, once the form is organized into the following sections:

- Responsible for treatment;
- Purpose of treatment (which, in this case, consists of selecting the option "estudos clínicos observacionais (não interventivos)");
- Personal data contained in each record (identification of the type of data processed);
- Data collection (direct, if data were provided directly by the holders, or indirect collection, if data is collected through the physicians);
- Comunication of data to third parties;
- Interconnects of treatments;
- International flows of data to third countries;
- Deadline for storage of personal data;
- How is performed the right of data access (in person, writing or other);
- Measures in order to implement security (physical security measures and logical security measures).

The request also should include the following attachments: patient information and informed consent form, CRFs, study scales and the justification of the racial data collection (if applicable), and also the payment receipt copy to CNPD. This fee payment receipt copy must be sent to CNPD within a maximum period of 3 working days.

4.3.4.2 Investigational site submission

To initiate a study in a specific site, we will have to obtain the approval of the CNPD but also the approval of two entities (if applicable): Local EC and Local AB. For this, we need to prepare and submit some essential study documentation such as:

- Protocol last version and amendments (if applicable);
- Signature page of the protocol and amendments (if applicable);
- Patient information and informed consent form and amendments (if applicable);
- CRF (draft is acceptable) and;

- Other documents, if applicable, such as clinical assessment scales, diaries, questionnaires, pharmacovigilance forms, among others;
- *Curriculum Vitae* (CV) of the investigational team (but at this stage, is usually satisfactory for submission only the signed and dated CV of principal investigator);
- Financial and/or investigational agreements, if applicable;
- Delegation letter from the sponsor to the CRO;
- Authorization from head of departement and even, if applicable, a statement by Principal investigator and;
- The notification or approval of CNPD.

This process however is not the same for all investigational sites because, for hospital cases for example, there are hospitals who demand some specific documentation (namely, EC specific forms, AB specific contracts template and statement from Principal Investigator), which requires that the monitor/ monitoring team seeking information about the existence of such situations and adapt the documentation for study submission for the applicable site. Once submitted, the study will be evaluated, at least, by the entities referred above, but this evaluation period may be different depending on the hospital, since, among others, there are hospitals with a lower frequency of EC/AB meetings for evaluate the submited studies. On the other hand, in the evaluation process, the local EC/AB may also emit questions, which can delay the approval process of the study in the hospital in which this will occur. However, this “delay" can be attenuated if the answer to the questions is celere, what might be possible if there is a contribution of the investigational team motivated and available in order to accelerate the study authorization in each of the correspondent sites.

Regarding the hospitals submissions, I had the opportunity to perform many submissions to a variety of hospitals (in continental Portugal and also in the Islands). In this way, it was possible for me, to verify the existence of specific requirements and procedures in some hospitals and prepare all documentation in order to meet such requirements. For example, I could verify that some hospitals had investigational departments that centralize submissions therefore, all the documentation should be delivered in such investigational department, but I could also verify that there were cases in which the study process would have to go towards two differents hospitals because the EC and AB of the hospital group was situated in two differents hospitals (EC is situated in one hospital and the AB is situated in another hospital), so it is very important to take this into account when we prepare the documentation. Additionally, I could understand that there are hospitals who demand some specific documentation (EC specific forms, AB specific

contracts template and statement from Principal Investigator, among others) and/or only accept the submission if there are also delivered of all the documentation in electronic format/CD-ROM.

After this submissions, for different studies that I have been involved over the past 9 months, I also perform, on a regular basis, many contacts with local EC/ AB (mostly with the secretariat of the AB) to follow-up the study evaluation process, in order to provide information to the monitoring team, sponsor and investigational team, if applicable.

Still on this topic, it should be noted that even though the study obtains the necessary approvals, in the case of amendments, it can be necessary that the study be re-evaluated and be given a new approval.

4.3.5 Preparation of the study initiation

Once obtained the final approvals from the respective entities (EC/ AB/ CNPD) the study is finally authorized to be conducted, so for it could realy happen, it is essential to have all documentation prepared in order to be possible to distribute for the investigational team so that the study may be initiated. In this sense, I have been involved in the collection and preparation of all the necessary materials (including preparation and/or collaboration in the PowerPoint presentation of the study to be made to the investigational team). The preparation of the study initiation also include the preparation of files (Investigator Files) that will be delivered to all sites as well as the files that will be in the kept by the CRA, at Eurotrials office, containing essential study documentation (Trial Master File).

The preparation of these files, is also a fundamental task as, in accordance with the existing guidelines, the essential documentation of research activities should be securely maintained to provide evidence of activities, for example, in the case of a regulatory inspection or an internal or external audit (promoted by the sponsor). Here it should be noted that in some studies, the documents may have to be sent to a central file (not located at Eurotrials office), but in non-interventional studies this is not so frequent because most studies are at a national level.

During the internship, I prepared, autonomously, these files and I was responsible for keeping them organized and updated. So, I had the opportunity to verify that indeed the conducting of non-interventional studies also generates a lot of documentation and just how important it is to keep it properly filed and updated, especially in studies that involve many sites and many investigators.

4.3.6 Site initiation

After all these stages already mentioned above, the next step is to schedule a meeting (presentialy or remote) with the study investigators in order to initiate the study because the initiation vist can only be performed after the respective approvals have been obtained.

In the observational/non-interventional studies it is common that the training is given during meetings at the investigational site, by phone/web or during a national/regional meeting of investigators where all study procedures are explained and all materials are distributed. However, regardless of the initiation visit/call be made for each investigational site or through a national or regional meeting, the main objective are the same: ensure that all aspects of the study are discussed with the Investigator and other key investigational site team members involved in the study (for example, training the site staff in the study protocol; patient information and informed consent form; information provided to the patient, safety reporting procedures to follow in the event of an AE/SAE, study specific procedures; recruitment period timelines; monitoring procedures; co-monitoring visits/calls, audits and inspections and highlighting CRF common errors and respective corrections; ensure that all the documentation is ready and archived, and that all information and resources are available, so that patient's inclusion may beginning as of that visit date on. During the Initiation Visit/Call, the study personnel will also be trained in study specific guidelines and regulatory obligations.

The beginning of the study is a critical step and it is essential that there is a training and capacity the investigational team for the implementation of the study in order to ensure that all information and procedures needed, were assimilated by the team in order to a correct start of the study. However, and as referred, those visits/calls can only be performed after the applicable national regulatory requirements have been fulfilled. For that reason, during preparation of an initiation visit/call, the CRA should confirm that all necessary approvals/documents to initiate the study are available, namely:

- Authorization from CNPD;
- Authorization from applicable local EC and applicable local AB where the study will take place;
- Authorization from head of department (but it will be not mandatory if he/she is simultaneously the principal investigator);
- CV of site staff known to participate in the study by the time of Initiation Visit preparation;
- Signature page of the last version of the protocol, and amendments, if applicable, and confidentiality agreement signed by the principal investigator;

- Contracts between sponsor/designee and principal investigator/institution, if applicable;
- Any additional required local documentation, in accordance with specific institution regulations;
- Any other document according with local requirements.

However, depending on the type of studies to be implemented, it may not be necessary some approvals/documents to initiate the study.

These visits are usually conducted by the CRA of the study and sometimes the sponsor is also present. From the site it is very important to have all the team members that will be involved in the study. The principal investigator, must be present and the greatest possible number of elements of the investigational team since during the initiation visit, are discussed important topics such as:

- Protocol presentation;
- The process for obtaining the informed consent form;
- Presentation of CRFs and/or study questionnaires;
- Notification of adverse events (depending on the nature of the study, the approach to this topic can be more or less thorough);
- Explanation that all information collected within the scope of the study, should be recorded in the clinical process;
- Procedures for communicating with the study CRA;
- Collection of pending documentation, forms and signatures, if applicable.

However, although there are several different methods concerning the presentation of the study, the most common procedure is to perform study initiation visits to each site. So, during my internship I was only involved in studies whose initiation visit was performed by CRA at all investigational sites, after the applicable national regulatory requirements have been fulfilled. Anyway, it is essential that this visit will be very well planned because it may be the first contact of the CRA with some of the elements of the investigational team and also may be the first contact of these with the protocol. Therefore, it is very important that all procedures are properly explained, and understood, and that all the issues are clarified for, after this visit, all the elements are able to begin the inclusion of patients. For this, I have verified that the CRA ability to capture the attention of the team, becomes a very important issue.

Following this visit/call and if applicable, the CRA must complete a site initiation visit report where are described the items that were discussed during the visit (namely, if study objectives,

study protocol, patient information and informed consent form, CRF completion and corrections, treatment period and study procedures, serious adverse events/ adverse events reporting and follow-up, monitoring procedures, source documents, were or not discussed) the elements presents, the issues that eventually were pending (for example obtain a study staff CV, as well as others relevant informations namely regarding site personnel motivation, commitment, performance and training). Site initiation visit report can be reviewed and discussed with the PM, if applicable, and must be sent to sponsor for their knowledge/ review.

4.3.7 Monitoring / Quality control

During the recruitment phase and/or during the conduction phase of the study, it is essential to monitor all performed activities. However, such as in the initiations visits, in observational/non-interventional studies, is the common existence of different methods for the conduction of such monitoring activities. So, these can be made in the investigational site (throught a visit) or can be done remotely (by phone contact). Anyway, whenever possible, these must be performed particularly with the aim of:

- Assess the recruitment and continuous patient participation and if they meet the criteria of eligibility;
- Make the quality control of performed activities:

  - To verify the obtention of the informed consent form before collecting any other personnal data;

  - To verify the correct fill of the CRFs (identification of discrepancies, errors or inconsistent data that must be corrected by the investigator);

  - To verify the correct registration of information in source documents/ to monitor the data collected for the study – Source Data Verification (SDV), that is, perform a comparison between the CRF and the source data that can be found in source documents (medical records, laboratory results, among other documents), to ensure the data is accurately captured in the CRF;

  - To verify the compliance with applicable law.

- Assess if the pharmacovigilance procedures are being fulfilled;
- Verify if only are participating in the study, the qualified/trained elements, whose activities in the study were authorized by the principal investigator;
- Collection of CRFs, in case of the same are in paper format;

- Update the investigator file according to the applicable SOPs;
- Motivate the investigational team;
- Evaluate and resolve the potential difficulties of the team;
- Assess whether the pending actions resulting from the last visit were resolved and, if not, perform the follow-up until they are resolved.

So, the main objective of these visits/calls is also oversee the study progress, and to ensure that is conducted, recorded, and reported in accordance with the protocol and also in accordance with the ethical principles laid down in the Declaration of Helsinki, according to GPP, GEP, and/or GCP and also applicable local regulatory requirements and laws. After these visits, and depending on the study and sponsor, will also be performed a visit report which describes the items that were discussed during the visit and potential discrepancies detected, the study team elements that were present, the issues that eventually remained outstanding and those that were resolved, as well as other relevant information.

Despite the importance of all these activities, it is possible to understand that, if the monitoring activities are done remotely, it will be more difficult to verify some of the aspects previously mentioned. In the same way, although it is carried out a monitoring visit to the investigational site, may be some pending situations whose resolution may have to be carried out remotely but very often, this visits are extremely important. So, the existence, or not, of face-to-face visits will be determined by the study sponsor and may even be more than a monitoring visit to each site, according with what is stipulated in advance by the sponsor. It should also be noted that, in studies in which is not predicted the existance of on-site monitoring visits, throughout the study, is sometimes agreed the possibility to perform quality control visits of the data generated at the end of the study or during the study to a sample of the investigational sites, randomly selected. The quality control visits have the purpose to verify all patient data included, in order to assess the quality of the recorded information on the CRF in comparison with the various source documents (clinical process; laboratory results; questionnaire of QoL; patient diary, as applicable). In the case of a selected site, the records of clinical processes for validation of information should be available.

In contrast to the described in the section of the initiation visits, with regards to monitoring activities, I had the opportunity to participate actively in a quality control visit where I performed some of the activities mentioned with a special focus, as expected, at the point on the control of quality of activities (namely, assess if patients meet the criteria of eligibility and verify the obtention of the informed consent form before collecting any other personnal data, the correct fill of CRFs, the correct registration of information in source documents and if only are

participating in the study the qualified/trained elements whose activities in the study were authorized by the principal investigator; assess if the pharmacovigilance procedures are being followed and update the Investigator File according to the applicable SOPs). During these 9 months, I was also involved in several in-house monitoring activities such as: support in the preparation of monitoring visits; verification of the correct completion of CRFs on paper format and later queries emission well as the follow-up to the resolution; contact with electronic CRFs and verification of some data inserted; quality control of documents contained in the *Trial Master File Site Doc* and sending of missing documents and materials required for the recruitment continuation and to the follow-up of patients. I also participated actively in the processing of payments to investigational sites; in preparation of pocket guides for investigators, newsletters and other tools for a better study management and monitoring.

4.3.8 Close-out the investigational sites/ study close out

Close-out visit should be the last visit of the study to the investigational site with the objective of ensure the adequate completion of the study procedures at that site and to make sure that the Investigator understands his/her continuing obligations.

This visit or call should be performed when the study is concluded (at the site or remotely), in accordance with protocol but also when sponsor decides to interrupt the study in a single or all the investigational sites and/or when the Investigator, EC, health authorities or AB, if applicable, request the interruption of the study or the investigational site participation in the study.

The contact made with each participating investigational site, in order to be officially close the site, may be through a visit, by phone or can simply be done through a notification letter, depending on the study and the previously defined by the sponsor. During the closing process a retrospective analysis of the relevant aspects of the study in general, and of the site in particular, should be made, including the total patients recruitment achieved, the investigator fees already received or to be received by the site (if applicable), and the period of the study documentation retention and archive conditions. Regarding this last point about the archive period and conditions, due to the fact that currently there is no legal standard regulamentation for observational studies, these deadlines are normally based on guidelines followed in each project, of which are example the GPP, which indicates that the data collected during an observational/epidemiological study must be preserved for a period not less than 5 years after the first publication of the results (after final report or first publication of study results, whichever comes later) (25). All the study documents, such as: study protocol and all approved amendments; a final report of the study; all source data; documentation adequate to identify and locate all

computer programs and statistical procedures used; copies of electronic versions of analytic data sets and programs, computer printouts, if feasible; correspondence pertaining to the study, SOPs, patient information and informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits, as applicable, should be kept in a safe place and with restricted access (25). Additionally, the study sponsor may indicate, periods of archive data, higher than the established by the above guidelines.

Depending on the type of the study, the CRA must ensure that the regulatory authorities and the local ECs are notified of the completation/ premature ending of the study and follow the local legislation regarding the specific procedures and timelines for any of these notifications to be performed (if applicable).

During my intership I followed, essentially, observational/non-interventional studies that were in the early stages, I had no opportunity to attend on any close-out visit. However, I have been involved in close out activities, namely in the process of following the resolution of outstanding queries, in order to later transfer CRFs for Data Management department of Eurotrials and, I also helped in sending letters to the hospitals AB/EC and to the investigational team, in order to notify the study termination. Additionally I also observed the procedure relating to a international study whose activities were premature ended by the sponsor decision.

4.4 Others activities performed

Even during the internship, I have been involved in some activities related to the company's quality assurance procedures.

An audit is a systematic and independent examination of the activities and documents related to a clinical study, which is performed to determine whether the activities were properly conducted and whether the data were registered, analyzed and reported with total accuracy, in accordance with the protocol, sponsor’s SOPs, with good clinical practices and applicable regulatory requirement(s) (12). Therefore, there may be two types of audits: internal or external. Internal audits are conducted by the company, according to the quality system implemented by the same, in order to ensure the quality of the studies conducted by the company's team. On the other hand, external audits are carried out by the initiative of study sponsors or by quality entities, of which, Eurotrials has obtained a certification (ISO certification, for example).

In this sense, I had the opportunity to be involved in the preparation of an internal audit that would be carried out in accordance with the internal quality standards of Eurotrials. This activity

was very important because it allowed me to understand closely how important is to have the documentation of the study properly filed, as well as to have the tools to facilitate the organization of the same. Moreover, once the Eurotrials is certified under ISO 9001:2008, during the internship period, I accompanied the ISO surveillance audit that occurred. Although, in this audit, the activities performed have been few, this allowed me to see that the main focus of this audit is distinct from those previously mentioned, since the ISO auditor wants to ensure, essentially, that ISO standards are followed and that the company continues to develop its activities with a view to improving the quality of them.

Finally, I also participated in some activities of the review company's SOPs by writing a draft of a new SOP for the Epidemiology & Late Phase Research department, so these activities were also allowed me to enrich my internship.

5. Discussion

The 9 months of internship provided a very enriching experience, both professionally and at personal level. Throughout these months, I could enhance the knowledge acquired during the master's degree in Pharmaceutical Biomedicine as well as acquire new knowledge, even because the previously acquired knowledge in master's degree was more directed to the interventional studies. Nevertheless, during this period I could put into practice many theoretical knowledge obtained during the first year of the master's degree so, I think that, it was an great tool to prepare me better for the working world.

In addition to the support obtained by the afore mentioned training, I could not fail to mention the importance of all elements of the Epidemiology & Late Phase Research department, who contributed much to the success of this internship, once they sought to integrated me in the ongoing projects, was always available to accompany me and clarify doubts and, was given me the opportunity to develop the aforementioned skills and helped me identify some weak points, in order to try to improve them. Moreover, was possible to verify that this environment of mutual help is not exclusive of the department where I was integrated because, in Eurotrials, there is a very good working environment, with equally good interaction between collaborators of different departments.

Regarding of the activities performed, during these 9 months, and unlike of what happened in the previous year where the company has received colleagues of master degree and has provided to them a multidisciplinary experience, this year I was only involved in activities performed by the Epidemiology & Late Phase Research department. However, I don't think that this was a negative aspect because I performed diversified activities and I could deepen, even further, the knowledge in the tasks performed in this department so, this internship prepared me very well to perform future tasks more independently. Still, although the activities performed are only under the scope of Epidemiology & Late Phase Research department, it was be possible to interact with other Eurotrials departments, because as CRA Late Phase in training, I performed some activities in articulation with other departments, namely with the Data Management Unit, such as transfer the CRFs for Data Management Unit and monitoring the queries emitted for them, after introducing the data in the databases. I also performed some activities in articulation with the Finance and Administration department under the management activities of the payments to be made to the centers and Investigators (where applicable); with the department of Clinical Trials whenever it was necessary to have information sharing, and even with the Quality department in activities related the audits preparation, when I had questions regarding quality procedures, and when I was involved in the activities of revision of the company's SOPs. This

interaction helped me to understand the importance of the interaction between different departments and the team work, in order to have studies well designed and successfully implemented and conducted.

As regards the perception taken along the performed activities, I have confirmed the challenge to be CRA since, the CRA plays a central role in the communication at all levels, not only with research teams but also with sponsor. The CRA has also the responsibility to ensure the proper conduct of the studies and therefore have to adapt to different requirements, different "publics", different stakeholders and studies very diversified in order to perform the function in the best way. In this sense, this experience also contributed to a better perception of the type of activities performed by a CRA and the challenges faced, particularly in the area of non-interventional studies.

Indeed, all activities described in section 4 – Ongoing studies and developed activities, have helped me to deepen my knowledge regarding to the conduct of observational/non-interventional studies and acquire new skills. By analyzing my internship, I recognize the importance of the start of the activities that I have described in section 4.2.2.1 – General training program, with general training in the company SOPs, the collaborator manual and other reference documents (GPP, GEP, Helsinki Declaration, ICH-GCP, local legislation, among others), because these trainings constitute a first tool, not only to the integration of the new collaborator but also to serve as a basis for the activities that will be performed later, since they will have to follow the existing legislation and/or reference documents and procedures adopted.

Regarding to the performed activities, the activity that where I was mostly involved was in preparation of submissions processes to the health authorities and subsequent follow-up of the evaluation of studies as well as in the preparation of material for the visits to the centres and in the management of the archive of the documentation generated during the study.

Regarding the studies submission activities, I can say that these contributed to understand the existing regulatory requirements and the differences that may exist, not only from type of centres, differences between sites, but also the differences depending the type of study to be implemented. By follow the submission activities, I also developed some skills including the communication skills with different stakeholders (EC/ AB, Investigators, sponsors). I could also verify that, in addition to differences exist in study submissions between different types of sites, there are also differences between sites of the same type, in the case of hospitals, for example, even if the same study is submitted for the same entities of each hospital, the approval times can be very different and can also be requested different documents and procedures. Still on the submissions, I realized how bureaucratic and slow can be to implement a study.

The other activities developed in-house also showed me how important are to have the documentation correctly archived, develop good monitoring tools (such as trackers related to the study evolution) and, preparing and report all the visits performed to the investigational sites. As regards to the investigational site and team, I also could understand that is not always easy to contact all the team and keep everyone motivated. This also happens because, although the observational/non-interventional studies are conducted during, and in accordance with, the clinical practice, many times, the investigators has no the availability that we would like. However, during this internship, it was possible to verify that, if the investigational team is motivated for the study, they will be more receptive and more available for contact with the monitoring team and, the study will be better conducted, so it is essential to be able to maintain the communication with team. In the same way, I verified the added value that is the integration of study coordinators, on the investigational teams, because it is an element more available and that can centralize the information from other team members.

During this internship as CRA Late Phase in trainee, I could contact with different types of protocols of different types of studies (around 15 study protocols, in several therapeutic areas - see Appendix B - Main studies ongoing during the internship), with different requirements and different designs and objectives, in different sites and, from different sponsors. Thus, I believe that this opportunity to be involved in many different studies, at all levels, and with different sponsors is a great advantage of being a monitors in a CRO. But, I must confess that initially it was difficult from me to disconnect from the requirements of clinical trials, because the first year of master's degree was more focused on clinical trials and, in the clinical trials, the procedures are more specific and better defined. The non-interventional studies (or late phase studies - studies with market drugs) have more procedures than the epidemiological studies (population based studies), and can allow the evaluation of large numbers of patients/consumers, document the actual clinical practice, allow heighten disease awareness, support research and scientific inquiry, cultivate key customer relationships and, generally are less expensive than clinical trials but, the regulatory submissions of them, can vary from country to country since the need to perform a full submission until perform a simple notification because there isn´t a harmonized legal framework for this kind of studies (65). While the supplements regulations and guidelines for non-interventional studies rapidly being changed and are far from being harmonized in the EU, it is necessary that the study stakeholders check with local authorities and/or ethics committee before starting non-interventional studies (65). This point was an difficulty detected during the internship because there is no harmonization of criteria for the studies evaluating from different local entities, which leads to studies that can be approved in some investigational sites, has be disapproved in others. Moreover, some local ECs when performing the studies evaluation have

different criteria in considering the same study has interventional or non-interventional. In this sense, I think it would be really very important to have a standardization of evaluation criteria.

Throughout this period was also important to verify the procedures regarding the retrospectives studies. Here although all the information can be extracted from the patient clinical process, I have verified that, similarly, it is expected that the patient go to a consultation, according with normal clinical practice, and is obtained his informed consent before being collected any data.

During these 9 months, I had the opportunity to work with different monitors (inclusively seniors) and everyone contributed, over the time, to make me more independent, and apt to correctly perform the activities with minimal supervision.

Throughout these months I increased the interest for this area and this experience allowed me to better understand the essential role of CRA and CROs in health research. It also gave me practical knowledge on how to properly submit, conduct, report, monitor and close-out the observational/non-interventional studies.

During my internship, what I enjoyed the most was the opportunity to meet so many studies with different regulatory requirements, be actively integrated in these studies. In the same way, I enjoyed to perform the activities described in the Chapter 4 - Ongoing studies and developed activities and the possibility to directly contact with so many different stakeholders. On the other hand, I did not had the opportunity to attend to a close-out visit and would like to had the opportunity to perform more visits to the investigational sites because I think it is, really very important to the CRA in training. However, at the end of the internship period I was invited, by Eurotrials, to assume the role of CRA of Epidemiology & Late Phase Research department. This invitation was very positive and will allow me, in the near future, the opportunity to improve my skills and to perform other tasks and more autonomously.

6. Conclusion

This report aimed to present the activities performed during the 9 months of internship in a Portuguese CRO, Eurotrials, Scientific Consultants, a company which provides services in the field of clinical research and specifically describing the activities of monitoring observational studies / non-interventional, developed during the internship, as well as the skills acquired.

The main objective of this internship was promote a "bridge" between the knowledge acquired during the first year of the master's degree, and the labour market and also serve as a source of new knowledge and prepare myself, to work in monitoring area.

Now I can conclude that the master's degree was an important tool to provide the basis for working in any of the related areas of clinical research and, particularly, for monitoring area. After these 9 months, I can also conclude that the internship allowed me to participate in different projects and give me a wide range of learning opportunities. So, not only allowed me to put into practice the knowledge acquired during the master's degree but also acquire new knowledge that prepared me to ingress in the working world. Throughout this period, I also acquire very clear notions of what are the functions of a Late Phase monitor and its role in the research studies.

For all of this and, in conclusion, according to established objectives, I can say that they were completely achieved.

In the near future, I would like to continue to work in this area and continue improve my skills and knowledge to be able to carry out any activity successfully and autonomously.

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Appendix A - Glossary

Glossary

CNPD (*Comissão Nacional de Protecção de Dados*) - Portuguese Data Protection Authority. The CNPD is an independent body, with powers of authority throughout national territory. It is endowed with the power to supervise and monitor compliance with the laws and regulations in the area of personal data protection, with strict respect for human rights and the fundamental freedoms and guarantees enshrined in the Constitution and the law (66).

Contract Research Organization (CRO) - A CRO can be described as an organization that is contracted by a sponsor to manage various steps in the drug development process, including conduct of preclinical studies, clinical study design and execution, data management, analysis, medical writing, and regulatory submission (67).

Epidemiological study - Any epidemiological investigation intends to study in human subjects the distribution and determinants of disease (38).

Good Clinical Practices – A standard, internationally recognized, for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (12).

Informed Consent – *"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form"* (12).

International Conference of Harmonization - Standardized norms followed by Europe, Japan and United States in order to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions (68).

Pharmacoepidemiology - Is the scientific backbone of therapeutic risk management the process of assessing a product's benefits and risks, and developing, implementing, and evaluating strategies to enhance the overall balance of such benefits and risks (25).

Pharmacoeconomic study - *"A pharmacoeconomic study evaluates the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, efficacy or enhanced quality of life) of a pharmaceutical product. Pharmacoeconomic studies serve to guide optimal healthcare resource allocation, in a standardized and scientifically grounded manner"* (69).

Pharmacovigilance - "*The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem*" (70).

Post-Authorization study - *"Any study conducted with a medicinal product authorized in the European Economic Area"* (71).

Primary Healthcare Centres - Public health services with administrative autonomy, consisting of several functional units (*Unidades de Saúde Familiares*, *Unidades de Cuidados de Saúde Personalizados*, *Unidades de Cuidados na Comunidade*, *Unidades de Saúde Pública*, *Unidades de Recursos Assistenciais Partilhados*) (72).

Qualification visit/call: Evaluation of investigator/team and site capabilities namely regarding human resources, equipment, logistical issues and recruitment potential for implementing the study (72).

Sponsor - A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization (73).

Standard Operating Procedures - Detailed, written instructions to achieve uniformity of the performance of a specific function (72).

Appendix B – Main studies ongoing during the internship

	Therapeutic area	Study description
1)	**Neurology**	National, non-interventional, multicentric study in the area of Epilepsy.
2)	**Infecciology**	National, observational, post authorization safety study, retrospective and prospective, multicentric study in the Human Imunodeficiency Virus area.
3)	**Lysosomal storage diseases**	International, observational, cross-sectional and retrospective, multicentric study in the Niemann-Pick type C disease.
4)	**Premature Ejaculation**	International, non-interventional prospective post-approval safety study in patients with premature ejaculation.
5)	**Endocrinology**	International, non-interventional post authorization safety study with patients with *Diabetes mellitus* type 2.
6)	**Haematology**	International non-interventional post authorization safety study with patients with multiple myeloma.
7)	**Reumathology**	National, observational, prospective, parallel group study in Rheumatoid Arthritis and Axial Spondyloarthritis.
8)	**Pain**	National, observational, multicentric study in the area of Chronic Pain.
9)	**Psychiatric and Neurology**	National, observational, prospective, multicentric study in the Alzheimer disease.
10)	**Psychiatric**	National, observational, cross-sectional, multicentric study in the Schizophrenia disease.
11)	**Oncology**	National, observational, multicentric study in the area of Renal Cell Carcinoma.
12)	**Endocrinology**	National, observational, multicentre study in the area of *Diabetes mellitus* type 2.
13)	**Cardiology**	National epidemiological study to evaluate the prevalence of Hypertension and salt intake.
14)	**Infecciology**	National epidemiological study to evaluate the national situation of chronic hepatitis B.
15)	**Osteoarthritis**	National, epidemiological study, observational, cross-sectional to evaluate the prevalence of osteoarthritis.