FILIPE MIGUEL ESTEVES CAMPOS
MONITOR DE INVESTIGAÇÃO CLÍNICA – ESTÁGIO NUMA FULL SERVICE CRO
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Relatório 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 Dra. Patrícia Margarida Real Pedrosa de Sousa da Costa Jorge, Clinical Project Manager na Unidade de Estudos Clínicos da KeyPoint, Consultadoria Científica, Lda e do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro
Dedico este trabalho à minha família e amigos pelo apoio que me prestaram.
o júri

presidente

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palavras-chave

Estágio, CRO, Ensaios Clínicos, Estudos observacionais, Monitorização, Biomedicina Farmacêutica, KeyPoint.

resumo

O presente relatório descreve a minha experiência na KeyPoint como estagiário na área de estudos observacionais. O estágio surge como um complemento prático aos conhecimentos adquiridos ao longo do Mestrado em Biomedicina Farmacêutica, na área em que pretendo desenvolver uma carreira profissional, os ensaios clínicos.

Durante os 9 meses passados na KeyPoint, Lda. participei em cinco estudos observacionais como Clinical Research Associate, nos quais vim a desenvolver competências técnicas que apenas uma experiência real pode oferecer. Pude ainda perceber como a monitorização de ensaios clínicos é fundamental para garantir os direitos e a segurança dos participantes e para garantir a fiabilidade dos dados recolhidos. Adicionalmente pude complementar a minha formação com atividades de Medical Writing, Gestão de Dados, Estatística e Inquiridor. Estas atividades complementares ajudaram-me a perceber o modo como uma Clinical Research Organization trabalha e deram-me uma perspetiva abrangente de áreas relacionadas com a monitorização.
keywords

Internship, CRO, Clinical Trials, Observational Studies, Monitoring, Pharmaceutical Medicine, KeyPoint.

abstract

This report intends to describe my experience at KeyPoint, as Clinical Research Associate for observational studies. This internship is a practical complement to the knowledge acquired in the Pharmaceutical Medicine Master’s, in the area of clinical trials.

During the nine months at KeyPoint I participated in five observational studies as a Clinical Research Associate, in which I got the opportunity to develop technical competencies that only a real job experience can offer. I also had the opportunity to understand how clinical research monitoring is fundamental to ensuring that the participants’ safety, well-being and rights are guaranteed, as well as ensuring the reliability of gathered data. Additionally, I was able to complement my training by participating in areas such as Medical Writing, Data Management and Statistics. These complementary activities helped me to obtain a comprehensive perspective of the role and dynamic of a Clinical Research Organization.
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Abbreviation List

AE: Adverse Event
CEIC: Comissão de Ética para a Investigação Clínica
CNPD: Comissão Nacional de Proteção de Dados
CRA: Clinical Research Associate
CRF: Case Report Form
CRM: Clinical Research Manager
CRO: Contract Research Organisation
CTA: Clinical Trial Assistant
EC: Ethics Committee
eCRF: Electronic Case Report Form
GCP: Good Clinical Practices
GVP: Good Pharmacovigilance Practices
ICF: Informed Consent Form
IMP: Investigational Medicinal Product
INFARMED: Autoridade Nacional do Medicamento e Produtos de Saúde I.P
IRB: Institutional Review Board
PI: Principal Investigator
SDV: Source Data Verification
SOP: Standard Operating Procedure
1. Introduction

During the period between September 2012 and June 2013 I had the opportunity to complete a curricular internship at KeyPoint, Lda, as an integrated part of the Master’s Course in Pharmaceutical Medicine at the University of Aveiro.

KeyPoint, Lda, hereinafter referred to as KeyPoint, is a Contract Research Organisation (CRO) that provides support to the pharmaceutical industry in the form of research services outsourced on a contract base.

The internship was focused on providing real experience as a Clinical Research Associate (CRA), also referred to as a Monitor, whose main function is to monitor clinical research. Despite the focus on the clinical trials or observational studies monitoring, I had the opportunity to develop activities in other areas relevant to the function of a CRO, as was the case with Medical Writing, Data Management and Statistics. Participating in so many different activities helped me to get a comprehensive perspective of the clinical research area, and I could understand the importance of each different area for a project’s success.

This report aims to describe all the activities as they developed, express what I have learned, and integrate my experience in KeyPoint with my personal development. For that purpose the present chapter will introduce the profile of the host company and my internship objectives, in order to help the reader better understand the report.

Subsequently, the Clinical Research chapter gives an overview of how clinical research is done, followed by the characterisation of the legal framework, identification of the key players in the area, and the importance of the clinical research associate, in order to finally portray the current condition of the clinical investigation area in Portugal.

After outlining the clinical research area, Chapter 3 “On-the-job training” details all the activities carried out during the internship, with special emphasis on clinical trial monitoring activities. Subsequently, in the chapter “Discussion”, there is an evaluation of the importance of all acquired competences during the on-the-job training, an assessment of the difficulties found and how they enabled my personal growth and, finally, a discussion on the contribution of the academic background to performing the assigned
tasks. After critically appraising the internship, the fourth chapter “Conclusion” gives my final thoughts about the experience acquired and the skills and knowledge developed.

1.1. Hosting company profile

Grupo KeyPoint operates in the scientific consulting and education domain. Presently, the group has two core business areas: KeyPoint CRO Scientific Consulting and Forpoint – Health Training and Innovation Institute.

The group began their success with the KeyPoint CRO founded in 1999. It was in 2003 that the company extended its scope of action to areas like Epidemiology, Data Management, Statistics and Medical Writing. (1, 2)


In constant growth, the company keeps providing new solutions to fulfil the clients’ needs, creating in 2005 Forpoint with the intention of providing training in the areas of expertise that characterise the group. (2)

In 2007 the KeyPoint Group was formed in order to encompass the growing diversity of the company, which had an addition of two new groups: Point2Point, which provides services in the scientific health marketing area, and dotPoint, which offers technological solutions in the health area.

Unfortunately, the exponential growth of the KeyPoint Group was punished by the economic crisis that affected the entire country, nowadays counting only with the subgroup KeyPoint CRO, where my internship has taken place and for which the organisational chart is shown in figure 1, and the subgroup ForPoint.
KeyPoint CRO has the following business areas:

- Development and follow-up of clinical trials from phases II to IV;
- Implementation of observational studies in hospitals, primary health care and in private clinics;
- Implementation of epidemiologic studies;
- Perform pharmacoeconomic evaluations to support reimbursement status requests and to evaluate potential medicines for exclusive use in hospitals;
- Redaction of scientific articles, posters, abstracts, translations and development of protocols, informed consents and other documents related to the development of observational and clinical studies;
- Statistical support;
- Regulatory Affairs, through the development of expert reports;
- Resourcing, through the outsourcing of specialised professionals;
- Evaluation and monitoring of health strategies;

Figure 1 - KeyPoint CRO Organisational Chart. Adapted from KeyPoint Quality Manual (4)
In turn, ForPoint has the following business areas:

- Training in clinical investigation;
- Education in behavioural health;
- Post-graduations in clinical investigation;
- Books and other technical materials;

The clients of KeyPoint Group come from four main areas: i) the pharmaceutical industry, ii) the food industry, iii) entities related to the health sector as associations, institutes, etc. and iv) individual clients such as physicians, among others.(6)

During the internship I was able to work in the clinical trials unit, a section of KeyPoint CRO with a team consisting of a Clinical Business Manager, a Clinical Group Manager (both representing Clinical Studies Coordination), three Project Managers, six Clinical Research Associates (among whom I was included), and two Clinical Trials Assistants.

For the customers’ benefit, all the activities performed by the KeyPoint Group are defined by three essential ideals: (4)

- Helping Portugal become a pole of attraction for the realisation of clinical trials, through the promotion, refinement and development of investigational studies;
- Investing in innovation and creativity, developing and disseminating campaigns of scientific health marketing;
- Making health education a priority toward the enhanced valuation of the participants in this sector;

1.2. Internship Objectives

Prior to beginning the internship, there were a few general objectives and transversal key competences that I expected for a professional experience in the clinical research area:

- Adjust and develop a work-related sense of responsibility;
- Develop attitudes conducive to effective interpersonal relationships;
- Obtain field expertise useful for a professional career;
- Creation of a job-related network;
• Learn time-management skills and to prioritise tasks.

After acquainting myself with the profile of the host company and in order to make the most of this experience I defined the following objectives to be achieved during the internship:

Primary objective:

- To acquire knowledge in the clinical monitoring area, and to acquire soft and hard skills relevant to professional growth, through a professional experience.

Secondary Objectives:

- To understand how a CRO operates, and to comprehend the role of a CRO in a scientific investigation.
- To gain expertise in areas complementary to monitoring activities, such as Medical Writing, Data Management and Statistics, and to understand how they interrelate in the development of a project.

As a complementary part of the highly specific Master’s course I had great expectations regarding the practical approach to this experience inside a full CRO. But it was only after assessing the internship approach that I defined other personal goals such as:

• Obtain autonomy through the application of the knowledge acquired in the Master’s course and in the initial on-the-job training;
• Know, in practice, how an observational study is developed, from the initial idea to the delivery of the final report;
• Integrate legislation and guidelines into on-the-job activities.
• Incorporate the quality control system in daily actions.
• Apply and further mature a critical thinking in order to react efficiently and effectively to solve daily monitoring problems.
• Learn to manage projects from different therapeutics areas.
2. Clinical research in Portugal

The present chapter gives a generic approach to the concepts of clinical research, addressing the different study types and their usefulness, followed by a brief explanation of the applicable international and national legislation when implementing and conducting a study, and by the definition of each stakeholder involved in the clinical research. Additionally, the role of the CRAs and their importance in the conduct of clinical research will be emphasized, given that this was my internship area. Finally, the framework of the clinical research status in Portugal will be provided.

Clinical research is defined as a research conducted with human subjects, performed by an investigator, in order to gain knowledge about a predetermined hypothesis. The hypothesis under study can be related to human disease conditions, human behaviours, effects of therapies, interventions and diagnostic methods. (7)

Clinical trials and observational studies are the two main approaches to clinical research.

2.1. Observational studies

Observational studies or non-interventional studies are a particular type of clinical research in which there is no intervention given to the patient; these studies are limited to observations, without making changes to the patient’s routine.

According to the ICH Good Clinical Practices, for a study to be considered non-interventional it must fulfil the following requirements:(8)

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- 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 are applied to the patients and epidemiological methods are used for the analysis of collected data.
Non-interventional studies can be defined by the methodological approach; if the study is limited to a research or review of records of events in the past, it is considered retrospective; however, if the study involves primary data collection it’s called prospective, provided that it fulfils the requirements listed above. (8)

There are two common designs for observational studies: cross-sectional or longitudinal, which in turn is subdivided into cohort and case-control studies:

1. **Cross-sectional studies**: often described as a clinical picture at a given point in time of a group of individuals, this type of study collects all information in a single moment in time or over a very short period. The purpose of the study is to describe the population with respect to an outcome, finding its prevalence. (9)

   **Main advantages:**
   - Relatively inexpensive and reduced time consumption;
   - Ideal to estimate the prevalence of an outcome of interest because the sample is typically taken from the whole population;
   - Can assess multiple outcomes;
   - As it is a snapshot, there is no follow-up.

   **Main disadvantages:**
   - Difficult to provide causal interpretations;
   - As it is a snapshot, the same study can provide different results at other points in time;
   - Prevalence-incidence bias. Any risk factor for which the outcome is death will be under-represented.

2. **Longitudinal studies** for which the time sequence is relevant, divided into two types:

   2.1. **Cohort studies**: a study in which a group of subjects, selected as a sample, is studied over a period time. Just as in a cross-sectional study, information is gathered about the outcome of interest, but in cohort studies subjects are followed over a period of time. The period of time can be from the present to the future, a
prospective cohort study, or it can look at medical events which occurred in the past up to the present, a retrospective study.(10)

Main advantages:
- The temporal dimension: it provides the possibility to determine causality between an exposure and the outcome;
- Useful for multiple outcomes;
- Good for studying rare exposures;
- Has the sensibility to document change in exposure and outcome over time;
- Incidence of outcomes can be measured.

Main disadvantages:
- Costly (although less so for the retrospective variation);
- Possibly time consuming, especially if the outcome is age-related;
- Requires accurate records for retrospective studies;
- For rare outcomes, requires large samples;
- Predisposed to dropouts;
- Selection bias;

2.2. Case-control studies: Just like cohort studies, case-control studies are intended to establish an association between the exposure and the outcome. The sample is chosen at the onset time of the outcome and, only afterwards, the causal factor is assessed retrospectively. In this type of study there are two types of subjects: the cases, a group of subjects that have the outcome; and the controls, a second group of subjects that do not have the disease. The background of the two groups is compared regarding exposure to the specific factor being studied.(11)

Main advantages:
- Quick and cheap;
- Ideal to study rare diseases.
Main disadvantages:

- Susceptible to potential bias and confounding factors;
- Difficult to choose the subjects for each group;
- No information about the time-frame of exposure and outcome;
- Inefficient in studying rare risk factors;
- Not useful to calculate the incidence, as it is not based in the population.

2.2. Clinical trials

The development of a medicine is still a process with high consumption of resources and time and is traditionally constituted by two broad stages: the discovery and the development.

The stage of the discovery is characterised by the extensive study of a disease, the definition of therapeutic targets and for the validation of new molecules with activity against the targets.

The development stage can also be divided in two parts: non-clinical development and clinical development of the medicine. Before the new lead compound is tested in humans, it must undergo a pre-set schedule of non-clinical studies, such as in vitro toxicology, or animal toxicokinetics, intended to define its preliminary safety and efficacy. This non-clinical stage usually precedes the clinical development stage, which is constituted by clinical trials traditionally classified as Phase I to Phase IV. (12)

ICH-Good Clinical Practices (GCP) defines clinical trials 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.”(8)

Phase I clinical trials, also referred to as “human pharmacology studies”, is the phase in which the medicine is tested in a small sample of 10 to 100 healthy volunteers, with the
objective of proving its safety and tolerability. In special cases where the toxicity of the
new medicine is known to be high; for example, with cytotoxic medicines, the phase I
clinical trials are conducted in a small group of patients. (13)

Phase II is also called “therapeutic exploratory studies”, and has the objective of
determining the dosages (posology) while gathering information on the efficacy profile of
the new medicine. It is divided into two sub-phases: (13)

- IIa: clinical pharmacology in a small number of patients, ranging from 10 to 200,
  who have the intended disease in order to assess the pharmacodynamics,
  pharmacokinetics and concentration– response relationships.
- IIb: larger trials with several hundreds of patients to properly evaluate the
  concentration–response relationship and increase understanding of the efficacy,
  safety and tolerability.

Phase III aims to demonstrate the therapeutic benefit of the investigational product and
also known as “therapeutic confirmatory studies”. As it is the final phase before the
approval, these studies must sustain the clinical trial application, establishing the safety
profile of the drug and the dose-response relationship. In order to do so, these trials are
usually very long, involving a great number of patients. (13)

Phase IV trials, the post-authorisation trials, are performed after the new medicine is
approved, when it is already is marketed. These studies follow the “therapeutic use” of the
medicine in a non-ideal population using normal medicine practices, and therefore refine
the understanding of the benefit-risk ratio and the dosing recommendations. Additionally,
due to the new medicine being distributed to a great number of patients, with concomitant
comorbidities, less common side-effects and medicine interactions are more easily found,
refining the recommendations for its use. (13)

This traditional view of the clinical trials from differentiated phases from I to IV is falling
into disuse, preferably replaced by the terms “Human Pharmacology”, “Therapeutic
Exploratory”, “Therapeutic Confirmatory”, and “Therapeutic Use”, which remove the
sense of a unique continuous process given by the phase’s denomination. Studies can be
overlapped or it is possible to “go back” and perform more studies from a prior stage in
order to gather more information for the following stages. Figure 2 demonstrates the
relationship between the definition by types and the definition by stages. (12)
2.3. International and national legislation

The pharmaceutical industry is regarded as one of the most regulated industries in the world for the sake of ensuring the safety of the patients. Clinical trials, as a representation of the first steps to bringing a new medicine to the market, are not an exception and are highly regulated. In respect to the implementation and conduction of a clinical trial there are rules and regulations to apply which are provided by the country where the trial is being executed, in conjunction with other international legislation, guidelines and recommendations.

For instance, all medical research must follow the Declaration of Helsinki, a successful combination of the protection of Human rights and a comprehensive statement on the ethics of human research, laid down by the World Medical Association after the publication of the Nuremberg Code. (14)

In order to harmonise with international medicine guidelines, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created in 1990, and its recommendations are, without a doubt, an important contribution to pharmaceutical development. The ICH – Good Clinical Practice are an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. (15)
If the study is being conducted in United States of America, the applicant must follow the Food and Drugs Act of 1906, the legislation in force, and follow the rules and regulations issued in the US Code Federal Regulations (CFR), especially Title 21 of the CFR, which is reserved for the rules of the Food and Drug Administration (FDA). The FDA is the US agency responsible for ensuring the safety and effectiveness of all medicines, biological products (including blood, vaccines and tissues for transplantation) and medical devices, among other health related products. It also offers guidance on how to conduct clinical trials through a comprehensive set of guidelines. (16-18)

In Europe the European Commission is responsible for issuing all directives and recommendations that must be followed when implementing a clinical trial in a European Country. As a standard, those directives must be translated and transcribed into the law code of each member state. Guidelines and other guidance documents are issued by the European Medicine Agency, and through the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) new scientific guidelines for clinical trials are prepared, in consultation with regulatory authorities in the member states.

In Portugal, to implement a clinical trial it is necessary to be mindful of the following European Commission Directives and national legislation, in addition to GCPs and the Helsinki Declaration.

**European Commission Directives:**

Directive 2001/20/EC, of the European Parliament and of the Council, of 4th April 2001: provides a common legal framework for all member states in what is considered the application of good clinical practices in the conduction of clinical trials. This directive was transposed into the law of each member state, thus, in the Portuguese national the Law 46/2004, of 19th of August. (19)


Directive 2005/28/EC, of 8th of April: Establishes the principles and details the guidelines on good clinical practices for investigational medicinal products, as well as the compulsory requirements for the manufacturing and importation of medicinal products. The Decree-Law no. 102/2007 of 2nd of April is the Portuguese transposition of the present directive. (22)

National Legislation:

Law no. 46/2004, of 19th of August: institutes the legal framework for the conduction of clinical trials using medicines for human use. (23)

Decree-Law no. 176/2006, of 30th of August: Also called the Medicinal Product Statute, the present decree-law establishes the legal framework for marketing authorisation and its amendments, for the manufacture, import, export, marketing, labelling and information, advertising, pharmacovigilance and use of medicines for human use and their inspection. (24)

Decree-Law no. 102/2007 of 2nd of April: Lays down the principles and guidelines for good clinical practices concerning investigational medicinal products for human use, as well as the requirements for the manufacturing and importation of those products. (25)

Law no. 67/98, of 26th of October: The personal data protection law establishes the rules within the principle to process personal data with respect for the privacy, rights, liberties and fundamental guaranties. It transposes the Directive 95/46/CE, of 24th of October, regarding the protection of the personal data of individual subjects. (26)

In order to implement a clinical trial in Portugal it is necessary to obtain approval from the National Competent Authority, the National Authority of Medicines and Health Products – INFARMED, and to obtain a favourable opinion from the Independent Ethics Committee (Ethics Committee for Clinical Research – CEIC) and from the National Committee for Data protection (CNPD).

To implement an observational study in Portugal there is no specific regulation to follow, but it is necessary to obtain authorisation from CNPD, for which it is necessary to abide by the Decree-Law no 67/98 and the Deliberation no. 227/2007, applicable to the treatment of
personal data in the scope of investigation studies in the area of healthcare. It is also necessary to obtain authorisation from the Institutional Review Board and Board of Directors of each study site. The Good Epidemiologic Practices (GEPs) developed by the IEA-European Federation with the objective of highlighting the general ethical principles and the importance of informed consent, as well as the rules of good behaviour when processing personal data, documenting and publication of data from an epidemiological study, and the Good Pharmacoepidemiological Practices (GPPs), issued by the International Society of Pharmacoepidemiology, proposing the practices and minimum procedures to be assured in order to guarantee the integrity and quality of the pharmacoepidemiologic investigation, should be used instead of the GCPs. (27, 28)

2.4. Principal stakeholders in clinical research

Clinical trials demand the participation of a variety of stakeholders, who interact and work together, in order to successfully develop a project:

**Sponsors** are the entities with the responsibility to conceive, finance, manage and execute the studies. The implementation and execution of the studies can be subcontracted.

**Study Sites** are health entities like hospitals, primary health care centres, private clinics or laboratories with the capacity to develop clinical studies. In order to do so, it is necessary to have an investigational team and all necessary materials.

**Contract Research Organisations** are the entities subcontracted by the sponsor to implement clinical trials and to manage them: they act in the area of regulatory affairs, clinical research management and monitoring, data management or even pharmacovigilance.

**Investigational teams**: Headed by the Principal Investigator, it is also comprised of co-investigators, study nurses, study pharmacists, study coordinators and laboratory personnel.

**Competent authorities**: In Portugal the competent authorities are INFARMED, the National Authority of Medicines and Health Products, CEIC the National Ethics
Committee for Clinical research and CNPD, the National Committee for the Protection of Data. Other entities that play a part in the approval of the studies are the IRB, Institution Review Board and the Board of Directors of each study site.

**Patients,** or healthy volunteers in the case of Phase I clinical trials, are key stakeholders as they consent to participate in studies. They are often represented by associations to the pathology concerned.

### 2.5. Clinical Research Associate

An element essential to clinical research is the Clinical Research Associate, also called the Monitor: according to the GCPs, the sponsor should monitor the study for the purpose of guaranteeing the safety and well-being of trial subjects and ensuring the reliability of the data gathered. (8)

The activity of monitoring is defined by the ICH-GCPs as the act of overseeing the progress of a clinical trial, ensuring that the trial is conducted, recorded and reported in accordance with protocol, standard operating procedures, good clinical practice and other applicable requirements. (8)

Thus, the monitors ensure that the rights and the well-being of human subjects are protected, the data reported is accurate, complete and verifiable, and that the trials are being conducted in compliance with the protocol, Standard Operating Procedures (SOPs), GCPs and other regulations.

In order to perform these activities, the Monitor should have clinical research and scientific knowledge, besides a proper familiarity with the investigational medical product, protocols, informed consent forms, and other applicable documents.

The CRA should act as the connection between the sponsor and the investigator, keeping in contact with both parties. He should perform pre-trial initiation visits, trial initiation visits, routine monitoring visits and close-out visits, during which he should:
- Verify that the investigator and his team have the adequate qualifications and resources to perform the study;
- Assure that during the study the investigator and his team maintain the qualifications and resources necessary;
- Establish that the laboratory and the pharmacy comply with relevant SOPs, and have all the characteristics required for the conduction of the study;
- Ensure the dissemination of the pertinent elements of the study protocol, investigator brochure and all other trials supplies, such as Case Report Forms (CRFs) and informed consent forms;
- Verify the compliance of the investigators with protocol, GCPs, SOPs and regulations;
- Verify that only eligible patients are being included in the study;
- Ensure that informed consent was obtained correctly;
- Perform source data verification (SDV) to ensure that the source documents and the CRFs are accurate, complete and well documented;
- Search actively for adverse events and determine if these are adequately reported within all applicable periods defined per protocol and by the GCPs;
- Ensure the correct archiving of the dossiers and of the documents which compose it;
- Report recruitment rate, trial progression, study problems, adverse events and site necessities and provide solutions.

When applicable, regarding the Investigational Medicine Product, the CRA must ensure that:

- The storage conditions are appropriate;
- There are enough quantities;
- The IMP is being dispensed to eligible patients;
- The subjects are given correct instruction on how to use the IMP;
- The transition chain is adequately documented: reception, dispensing and return of the medicine;
- Destruction or storage of the used medicine is following the sponsor SOPs;
2.6. State of the art

The benefits of clinical trials are clear: they improve health indicators, give early access to advanced treatments, improve medical care, develop scientific knowledge, reduce public expenditure and create jobs, among other things. (29)

Therefore, it is natural to see the pharmaceutical industry as one of the sectors with more expenditures in Research and Development (R&D) achieving 27.5 billion of Euros invested only in Europe and, in agreement with this number, the activities of clinical trials have grown 15% between 2008 and 2012.(29)

Despite the abovementioned advantages, and in counterpoint to the general statistics, the number of clinical trials submitted in Portugal has decreased 26.25%, from 2006 to 2012, by which time only 118 Clinical Trial Applications were submitted.(30)

The typical sponsor of the clinical trials is the pharmaceutical industry against a minimal investment of the academic area: only around 5% of all studies submitted in Portugal are from the academic area, but this number has remained relatively stable over the years, with an average of 7 studies submitted each year in the period covered. (29)

It is possible to conclude that the reduction in studies is due to a disinvestment of the pharmaceutical industry in Portugal: this investment of multinational pharmaceutical companies was 3.5 million Euros in 2012. The Portuguese pharmaceutical industry has little representation, with only around 1% of the clinical trials approved. Conversely, three international pharmaceutical companies assured about 41% of the clinical trials in 2012, recruiting approximately 59% of all patients included in all studies active in that period. (29)

Furthermore, of the 118 studies approved in the last year in Portugal, the Phase III clinical trials included sixty-eight studies, whereas the Phase I had almost no representation with only one study approved.(30)

Oncology is the therapeutic area with most clinical trials, followed by those regarding the nervous system and infectious diseases. Overall those three areas represent more than half of the clinical trials approved in Portugal.(29)

When comparing Portugal to other European countries, such as Spain, Italy and the United Kingdom, we can conclude that we have a small recruitment capacity – a lower number of
patients per clinical trial, a lower number of patients in clinical trials per 1 million people, fewer patients included per site, and fewer sites participating in each clinical trial. Due to the common use of competitive recruitment between countries, these factors strongly disfavour Portugal.(29)

However, clinical research in Portugal has to face many obstacles. First of all, clinical investigation is not yet recognized as being important for the improvement of healthcare and the economy. As a consequence of this lack of recognition, there is no strategy to stimulate, structure and develop the sector. (29)

Clinical trials still have a negative reputation, as shown by the use of terms with negative connotations like guinea pigs when referring to trial subjects.

Approval periods are one of the clearest drawbacks: on top of the current slow approval by CEIC and INFARMED, the IRBs and Management Boards can take months to approve a study or to accept a financial agreement. One curious example which partially explains the little representation of Phase I clinical trials in Portugal is the example of Health Canada, the Canadian agency of medicine, which approves a bioavailability study, the most common type of Phase I studies due to the high amount of generic medicines being produced, in only one week; whereas Portugal approves a similar study in roughly 60 days, the timeline of INFARMED and CEIC. The absence of a strategic vision and the depreciation of the potential of the clinical investigation can be attributed to the Director’s Board, a condition that further delays the approval of the trials. Finally, CNPD also has no defined timeline to approve the data treatment methods in clinical trials or observational studies.(29, 31)

Furthermore, there is an unused potential for the implementation of clinical trials in the primary health centres which, for now, are only used to implement observational studies for which the approval time does not have to be competitive, as is the case of investigator initiated studies. This unused potential is partially justifiable for the restrictive legal frame for the implementation of clinical trials, and also due to the primary health centres being only oriented to act as an assistance model to the hospitals, even lacking information integration systems with hospitals.
There is also an absence of a regulatory framework to disclose the clinical investigation to the patients and even to the investigators, which creates another barrier to patient recruitment.

The investigational sites themselves lack a structure to support investigation: the hospital departments or even the investigators become overloaded with the necessity of having to perform all the investigation related activities.

The effort of the investigator in performing clinical investigation is not recognized; neither is it merited in the career progression which, when associated with the delay or non-payment of incentives by the hospital administration, discourages the investigators’ participation in the clinical studies.

Moreover, there is a lack of support and legislation to encourage academic investigation and the development of investigator initiated trials, which justifies the low levels of academic trials declared by INFARMED statistics.

Finally, although there is the National Platform for Clinical Trials (PNEC), its utility is reduced; thus, the information for the stakeholders is scattered by a half-dozen sites, and communication with stakeholders is difficult.

In order to overcome these barriers, Portugal must design initiatives to further develop the clinical research area and become more competitive:(29)

The definition of a strategic plan for the sector, and revision of the process of approval for clinical trials and data treatment plans can foster time approvals.

In order to facilitate patient recruitment, the creation of legislation to regulate the divulgence of clinical trials and the development of an integrated system between sites are actions to take into account.

Additionally, the revision of the impact of clinical research on the career of investigators, and the creation of a better mechanism to financially compensate the trial participation may stimulate the involvement of the investigators.

Other initiatives to take into consideration are the revision of the incentive programs to Investigator Initiated Studies, as well as academic incentives, the creation of conditions
favourable for the development of clinical trials in primary health centres and the promotion of a central platform for clinical investigation, among many others. Despite the many flaws, there is room for Portugal to improve its performance in the clinical research sector but, in order to do so, it is necessary to unite all interested parties in this common goal, as the progress represents a mutual benefit, only achievable with a comprehensive set of initiatives.
3. On-the-job experience

After the introduction of the clinical research concepts, this chapter will describe the activities developed during the internship. It will begin to address my multidisciplinary training in other complementary areas, such as medical writing, data management, statistics and surveys, before providing the actual description of my experience in clinical monitoring. Each section (one for each of the separate areas) will begin with a simple explanation of the field of training, followed by a description of the tasks performed.

At the beginning of the internship I was asked to review the core set of guidelines with relevance to the upcoming training, as well as to read all SOPs for the company, in order to become familiar with all the processes and procedures.

An approach common to all the different tasks performed in the different areas where I had the pleasure of being included was the theoretical introduction to every task, for which I was supervised until reach autonomy to perform the tasks entrusted.

3.1. Medical Writing

Medical writing is a core business of KeyPoint, and is an area of high visibility and one which impacts on the client’s perception of the company. It defines the success of a project, since it is critical in the early development of a study, through the creation of a protocol and all related documents, and it also defines the success of a project, because it is by the act of producing scientific documentation that the research is displayed to all interested parties.

I had the opportunity to participate in different medical writing projects:

- Redaction of a protocol synopsis.
- Adaptation of a study protocol to country-specific requirements.
- Development on Site Initiation Visit presentations for various projects.
- Translation of official documents of governmental entities in order to keep project’s sponsors updated.
- Redaction of an abstract for an interim evaluation of the project being developed by KeyPoint.
- Collaboration in a Systematic Review, as the reviser of the data gathered.

In these activities I received an orientation from the Medical Writing Manager and from a Medical Writing Technician in order to receive close guidance. I also had the opportunity to attend a lecture on how to perform Systematic Reviews.

The refinement of the protocol and protocol synopsis gave me an understanding of the work that is necessary to correctly design scientifically valid study protocols. On the other side of the study-related activities, the refinement of an abstract and of a systematic review gave me an awareness of the importance of data presentation in study results. In summary, my passage by the Medical Writing area was educational, as I had the opportunity to apply all the knowledge acquired during the Master’s course and to see its practical application in the context of a CRO.

3.2. Data Management

Data management is the act of inserting, cleaning and processing the data obtained in clinical studies. In KeyPoint not all studies had an electronic CRF (eCRF), as was the case with the surveys performed personally, so it was necessary to introduce the data gathered into Microsoft Access databases for an easy cleaning - the elimination of erroneous data, elaboration of queries, etc. - to finally be processed and given to the statisticians.

I had the opportunity to introduce the survey data from two different studies to help clean an observational study database answering to data management emitted queries, and to help to process the data, assisting in data categorisation for an easier evaluation.

In summary, Data Management is an extensive and time-consuming activity, but is important in the process of delivering error-free data for evaluation.
3.3. **Statistics**

In clinical studies, statistics, besides being crucial to study design, represent the translation of great amounts of untreated clinical data into meaningful results, analysing and making it clear, and making it possible to draw practical and expressive conclusions.

My experience in statistics was limited to the drawing of conclusions from data treated by SPSS Statistics software in order to write an abstract, in close cooperation with a statistician. Despite the short amount of time spent on this area I could truly appreciate the work developed by the department of statistics, an area highly valued by KeyPoint.

3.4. **Survey activities**

KeyPoint has a depth of experience in conducting surveys, and I was invited to participate in two different survey projects:

- For a healthcare professional developing a thesis on the anaemia subject, I was asked to perform surveys on the general population, chosen randomly, in the district of Viseu. In addition to the questionnaire, the study involved gathering data on the subjects including haemoglobin, alanine transaminase (ALT) and aspartate transaminase (AST) levels through the collection of blood using a needle and performing an immediate analysis.
- For a company in the food industry, we performed surveys on children, in order to characterise eating habits.

Although these tasks were unrelated to the internship’s primary objective, they really helped me to develop communication skills crucial to my personal development as a professional who needs a high level of social interaction in order to perform his activities, because it is a truly difficult and challenging experience.
3.5. **Clinical Monitoring**

During the nine months spent in KeyPoint I had more exposure to observational studies. These studies represent a good share of the company’s portfolio of studies, and due to their relative simplicity when compared with clinical trials, they were the ideal area in which to gain experience on clinical monitoring requisites.

I had the opportunity to participate as Monitor in five observational studies in different stages of development; two of them in the oncology area, another two in the area of autoimmune diseases and the last in the cardiology area. I participated in other studies mainly in the role of observer in order to obtain experiences of events which had not arisen in the studies in which I actively participated. Table 1 summarises the studies and the different stages where I contributed to the projects. The Enbrel study is a prospective cohort post-authorisation safety study, in paediatric psoriasis. The FAMA study is a retrospective cohort study in atrial fibrillation, whereas the REMA study is a prospective cohort study in the area of breast cancer. In turn, the NEN study is a cross-sectional study in the area of neuroendocrine tumours, and finally, EPIC is a prospective cohort post-authorisation safety study in the area of plaque psoriasis.

It is my experiences gained through the different stages of development of an observational study that I present and describe in the following pages.
### Table 1 - Observational Studies and phases in which I actively participated

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Study pre-initiation:

When starting an observational study it is necessary to have the basic documentation:

- Study Protocol
- Protocol Synopsis
- Informed Consent Form
- Case Report Form

In the case of sponsored studies, these documents are generally already prepared and are disclosed in the study responsibilities handover for the CRO. In other cases, for studies undertaken at the initiative of an investigator, it is usually necessary to develop all of these documents and it is primarily up to the medical writing department to develop this pack.

There are some of the essential requirements, regarding documents, for the submission of an observational study in Portugal; generally, the study synopsis must be in Portuguese, as a requirement of CNPD and some institutional review boards/boards of directors of hospitals. Moreover, the CRF must be in Portuguese, especially if it will be fulfilled by the patient, as in the case of quality of life questionnaires, a common toll on observational studies. Finally, the Informed Consent Form must be always in the native language, out of consideration for the patient.

Although it is unusual, sometimes it is necessary to adapt some appendices of the protocol in order to reflect the country’s standards, as was the case in one of the autoimmune protocols, where there was a necessity to reflect the view of fundamental tuberculosis tests from the Portuguese Pulmonology Society.

Another document not always applicable is the financial agreement, which is prepared in advance to the site submissions. The financial agreement in observational studies normally covers only the dedicated time of the investigators and pharmacists in the study, because by definition, the study cannot implement any changes in the treatment of the patient. Thus, it is seen as the payment of a symbolic value, and not all of the studies require it.

Normally, industry sponsored studies have a financial agreement as an incentive, whereas academic or association sponsored studies are not paid.

The selection of the participation sites is normally done by the study sponsor, which defines in advance a list of potentially interested investigators. Generally, it is the sponsor
himself who makes the first contact, but this task can be delegated to the CRO. If the investigators are not pre-defined it is necessary to undergo the selection of sites:

From the experience of the CRO or the sponsor a rough list of potential study sites is defined, they are then contacted through the department’s director, in order to evaluate the following points:

- Evaluate the interest of the hospital in developing the study
- Identification of potential investigators interested and with the availability to participate
- Study Site conditions:
  - Human resources, such as study nurses and/or study coordinators.
  - For eCRFs, if the hospital has a connection to the internet, or a dedicated computer with restricted access.
  - Recruitment potential.
  - Primary assessment of Institutional Review Board (IRB)/Board of directors’ essential requirements (e.g. doesn’t accept submissions before CNPD approval, own financial agreement template, etc.)

After receiving a definition of potential investigators it is necessary to see if they are actually interested, through a study presentation. This could be done remotely or on-site. The main purpose is to give knowledge and information and to capture attention and sympathy for the study. The Principal Investigator is the targeted person – if an on-site visit is done, a pre-defined study team can be assembled if there is availability – in other cases it is the Principal Investigator who, after demonstrating interest, defines a team. The main points of focus for this presentation are the rationale and scope of the study, targeted population and number of patients planned for recruitment, inclusion and exclusion criteria, overview of procedures and the data intended to be gathered.

Finally, when the investigator confirms his interest in participating, it is necessary to sign and gather protocol signature pages, financial agreements and department director authorisations.

All gathered documentation and approvals should be archived in dossiers that should be kept up-to-date. The designation and content of these dossiers varies depending for whom it is intended:
- Investigator Site File: Specific for each site, it is the dossier kept by the Principal Investigator.
- Study Master File: Archived in the sponsor’s facilities, this dossier is intended to collect all general documents generated for and from the study.
- Site Master File: Also archived in the sponsor’s facilities, this dossier should include all study documents specific to each site.

A server should also contain all documents, including correspondence exchanged with the investigators, in order to guarantee that no document is lost. The server should have restricted access, and have backup copies.

The refinement and archiving of essential study documents is a task usually performed by the Clinical Trial Assistant (CTA), whereas the visits to assess the investigator’s interest and site capacity are realised by the CRA.

My experience in this role during the internship was obtained during my participation in an autoimmune study from the very beginning, in which I had the opportunity to elaborate on the study synopsis, taking for a basis the protocol, adapting certain parts of the study protocol to Portuguese standards, as was the case of the tuberculosis diagnosis. I also had to prepare the financial agreements using both site and sponsor templates, to provide study presentations to potentially interested investigators via phone with a follow-up presentation by email, and to gather the documents necessary to the study submission either on-site, or through correspondence. Additionally, I participated in the refinement of the three types of dossiers for a wide range of studies.

**Study submission**

An observational study submission, as already stated, is submitted to three authorities:

- CNPD
- Institutional Review Board
- Site Board of Directors

Due to the submission similarity between the Institutional Review Board and the site’s Board of Directors, both will be addressed in conjunction.
Under the scope of the Law nr 67/98, of 26th October, the Law of Personal Data Protection, it is necessary to request Authorisation from CNPD in order to perform activities that involve processing personal data. The submission to CNPD is made through the submission of an online form available on the entity website, the General Notification Form, which requires the following key information:

- Information about the entity responsible for the data treatment
- Objectives of the data treatment
- Description of the personal data to be collected
- Procedures for data collection
- Whether the data will be communicated to third parties
- Security measures to maintain the confidentiality of the records
- Information about the entity or persons who will have access to the records.

A fee must be paid to validate the submission, and all documentation needed (e.g. CRF) for approval should be forwarded by email with the identification code sent by CNPD after the submission.

I had the good fortune to follow a CNPD submission of one of the observational studies, helping to fill out the submission form. I noticed the necessity of anticipating giving an earlier justification for crucial questions (such as ethnicity, a common question in clinical studies), in order to avoid possible delays in the approval schedule.

**IRB and Director’s Board**

In order to obtain approval to perform the study on the site, it is necessary to submit the study to the IRB and the Director’ Board. This submission varies from site to site, so a timely collection of information about the site procedures is necessary before the actual submission preparation. Although the dossier of submission is equal for both site entities, sometimes it is necessary to submit two dossiers for independent evaluation. In my experience, the only document that is not required for the ethics committee, but is an essential requirement to the Director’s Board, is the financial agreement.

A list of common documents necessary:
- Sponsor, CRO and Investigator contact list
- Requirements for application of the study endorsed for both entities
- Protocol
- Protocol synopsis
- Protocol signature page
- Authorisation from the Clinical Director to perform the study
- Curriculum Vitae of the Principal Investigator
- Case Report Form
- Informed Consent Form
- Financial Agreements
- CNPD approval

The length of time for approval is uncertain: some ethics committees meet every fifteen days; others once a month, but there is no guarantee that the study will be evaluated in a meeting. There is a necessity to perform a close follow-up to obtain information along the process of evaluation.

The approval is formalised through the issuance of an approval letter stating the approval of both entities and, if it is the case, the financial agreement is signed. After the receipt of the letter, it is then possible to start the study.

If a protocol amendment is issued, it should be submitted to the site entities for further evaluation.

Acting as a CTA trainee, I had the experience of gathering information pre-submission about site procedures, constructing the submission dossiers, and actually submitting studies to different sites and performing a follow-up about the approval state of the studies for different projects.

**Initiation visit**

After obtaining approval for the conduction of the study, it is necessary to assemble a visit with the entire investigational team in order to present the study: the initiation visit.
This visit is intended to train the team in study protocol and deliver all study documentation, and the presentation should cover the following aspects:

- Study Title
- Primary and Secondary Endpoints
- Study design
- Study duration
- Study population
- Eligibility criteria
- Study procedures
- Case Report Form
- Informed Consent Form and information regarding Informed Consent
- Roles and responsibilities
- Good Clinical Practice
- Pharmacovigilance procedures
- Contacts of the CRA, Project Manager and Sponsor

In this visit the Investigator Dossier handover is generally done. In this dossier all study documentation is presented, with the copy of the Protocol, a copy of the protocol synopsis, the study logs, the CRF on paper (even if the CRF is electronic, for guaranteed data collection in the case of system failure), eCRF credentials, if applicable, copies of the informed consent form and all authorisations, agreements and declarations essential for the study application.

The study logs include the following forms:

- Study team responsibilities form, also known as the Signature and Study Staff responsibility log, or even the Delegation Log: this is where the responsibilities of the principal investigator, co-investigator, nurse and study coordinator, in applicable cases, are stated, and a signature of each participant is included in order to enable the authorised personnel to administer all study procedures.
- Study screening log: this is where all the potential patients for entry in the study are identified. Although this log is essential to clinical trials, in observational studies it is used only in certain cases.

- Study enrolment log: here all the patients actually enrolled are listed and the patient code is defined. This list should be the only document to contain actual identification of the patient and should remain at the site always, even after the study ends.

- Monitor Log, or Visit Log: this is what the Monitor signs when performing a visit, as a record.

- Adverse event tracking log: this is another log that is essentially used in clinical trials, but could be used in observational studies, especially in Post-Authorsisation Safety Studies. This form is intended to register all study medication adverse events.

- Deviation Log: this is used when study procedures are violated: this log is another example of a document essential to clinical trials, and used only occasionally in observational studies.

The responsibility for performing an initiation visit rests with the CRA or the Project Manager.

My experience in performing initiation visits was accomplished by observing two visits, one of them for clinical trial, and performing an observational study initiation visit for an oncology project.

**Study Follow-up**

The CRA is responsible for following each site and the progress, ensuring that the site meets the study objectives, respect the GCPs and guidelines, and follows the study procedures. There are two means of following the study: in-house monitoring and monitoring visits. The decision of how to proceed is influenced by many variables, such as agreement with the study sponsor, the actual need to monitor, the number of study subjects and study complexity.
In-house study monitoring

In-house monitoring activities encompass a follow-up by phone or email, a review of eCRF, query resolutions, development of newsletters, CRF training and clarification of study-related questions. In observational studies, due to the lower complexity of the studies, in-house monitoring is a frequently used and relatively inexpensive tool.

A close follow-up could be the key to a project’s success, and the ease of doing it by phone or email becomes an even better method to help the investigator meet the objectives than the personal visit.

A follow-up by phone/email should address the following topics:

- Assess investigators’ doubts or problems and provide clarification immediately or by email follow-up.
- Assess how many patients the investigator has in mind to include, or has already included, in order to evaluate recruitment objectives.
- Motivate the study team, and present ideas to improve recruitment, if needed.
- Inquire whether a new member was added to the study team and provide a reminder of study procedures, such as recording the new study member in the delegation log.

As already mentioned, a follow-up email can be sent in order to clarify questions, send necessary documents, or to solve other pending issues. A contact record with a small description of the most important topics covered should be created.

An update, after all study sites have been contacted should also be used to keep project managers and, in turn, the study sponsors, informed.

A review of the eCRF in order to find possible discrepancies can facilitate the monitoring visit itself, and can help find preventable systematic errors.

The creation of a newsletter can be a powerful motivation tool, in addition to being a good tracking instrument, helping the investigators to understand the efforts necessary to achieve the recruitment target and to keep up with study procedures, like filling in the CRF.

In KeyPoint in-house monitoring activities were a widely-used way to follow up the site visits, and for all the studies for which I was responsible, I performed these activities.
Monitoring Visit

The monitoring visit should be performed when the first patient is included, and if possible, during the inclusion to help the study team become accustomed with the study procedures or, if not possible, within two weeks of the first patient being included. They should also be performed at least every two months, depending on the site’s performance, study difficulties, recruitment rate, etc. The monitoring visits are indispensable during a project for which the CRF is on paper, as there is no possibility to follow-up after its completion.

Before the actual visit to the site it is necessary to do some background work, preparing the visit itself. As already stated, the revision of the eCRF is a fruitful activity, as the revision of protocol procedures, especially the eligibility criteria, is useful to verify the correct inclusion of patients. The revision of the last monitoring visit report can serve as a reminder of “chronic” site problems and any pending issues that need to be handled. Upon scheduling the visit with the investigator, key documents should be requested to be available during the visit, such as the CRF, the informed consent forms, source documents and investigator dossier with all necessary forms.

During the visit the CRA should evaluate the following aspects:

- The recruitment rate and any recruitment problems;
- Depth of knowledge of the study protocol by the investigators;
- Verify that the informed consent forms are correctly signed and dated;
- Check the inclusion and exclusion criteria of study subjects;
- Verify that the CRF is updated and correctly filled;
- Confirm that the logs are kept updated;
- Certify that the applicable guidelines and other applicable requirements are being used and enforced;
- Confirm that the study protocol procedures are being followed.
Three of the most crucial points of a monitoring visit are:

- The verification of the informed consent forms that must be correctly signed and dated by the investigator as well as the patient. The intention of the informed consent form is to testify to the authorisation of the patient to undergo the study procedures; therefore, this document must be completed perfectly.

- Source data verification, the corroboration of the content of the CRFs with the documents from where the information was collected, which is generally represented by the clinical records, is the task that ensures the veracity of all data.

- Investigator dossier review is another critical task because it allows the CRA to understand what must be updated. Logs are completed concerning documents that must always be up-to-date and in order to document all activities performed during the study.

After all visits it is necessary to fill out a visit monitoring report, in which all aspects of the visit are summarised, helping all parties to understand what was done, clarifying actions, and helping to define pending issues. A follow-up email with the monitoring report and a list of pending issues is considered good practice.

The tasks mentioned above are always performed by a CRA, and in my internship I had the opportunity to act as co-Monitor and as an independent Monitor in many visits from different projects.

**Close-out Visits**

The end of a study for a site is defined by the close-out visit. This visit should only be done when all files, both from the site and from the sponsor, have been reviewed, ‘synchronised’ and completed without pending issues. It is the last monitoring visit to the site and for this the following requisites must be met:

- Last patient’s last visit has already taken place;
- CRF has been reviewed and all the queries answered;
- Investigator dossier, site dossier and sponsor dossier are all complete with essential documents.
After the visit a notification for the Institute Review Board and for the Director’s Board must be sent giving notice of the end of the study, clarifying data about the study status, such as the number of subjects included, serious adverse events reported and any protocol deviations which occurred during the study.

The investigator’s dossier must be kept at the site for at least five years after the study’s closure. This period could be longer if the sponsor so desires.

The close-out visit is performed by the CRA, and as a trainee, I had the opportunity to close an observational study with many sites, resolving queries, filling all necessary logs and forms, archiving documentation (such as note to files, updating the study team and corresponding CV’s), among other more basic activities, which in the end gave me a thorough experience in this final stage of the study.

### 3.6. Experience in Clinical Trials

Although my experience in clinical trials was brief, this section is meant to give a summarised view of the clinical trials activities, emphasizing the differences between clinical trials and observational studies, and to share my involvement in those types of studies during my nine month internship.

**Site feasibility**

Site feasibility visits are similar to site selection in observational studies but, due to the need to administer a treatment, this visit must include an assessment of the laboratory and pharmacy conditions. As clinical trials can be very complex, a rigorous feasibility visit must be performed with rigorous, restrictive criteria.

The investigator must read the Investigator Brochure of the Investigational Medicine Product (IMP) and the protocol before agreeing to participate in the clinical trial. It is also usually required for the Principal Investigator to sign a confidentiality agreement.
Submission of clinical trials

In addition to the submission to CEIC and to centres, as happens in the observational studies, the law nº 46/2004 of 19th August states that is necessary to obtain a favourable opinion from the CEIC, the National Ethics Committee for Clinical Research, and from INFARMED, the National Authority of Medicines and Health Products, IP in order to realise a clinical trial.

Even before the submission to these entities, it is necessary to obtain a EudraCT number; the number that will be used to identify the trial, which is received through the registration of the clinical trial in the European clinical trials’ database. This number will be used to identify the trial. The application consists of the submission of basic elementary information about the trial, which triggers the reception of an email with the EudraCT number. Afterwards, the applicant can register the trial and obtain a XML file, which is necessary to submit the trial to the authorities.

The submission to the Portuguese authorities, CEIC and INFARMED can be done in parallel and, for both institutions, the submission is done in a mixed format of paper and electronic documents.

For CEIC the submission should follow the document “Instructions to the applicants for the submission of an opinion request to CEIC”(32) and “Instructions to the Applicants – CD-ROM organization”(33), and for INFARMED: the submission should follow the requirements established in the “Instructions to the Applicants of a Clinical Trial Application”(34) and “Instructions for the information electronic submission”(35).

In general, the documents necessary to submit in paper are:

- Cover letter directed to the President of CEIC and INFARMED;
- Proof of fee paid to INFARMED, according to Portaria 396/2005, of 7th April;
- Annex I (Clinical Trial Application Form) completed and signed by the submitter;
Also, in electronic format and in compliance with the folder structure defined by the verification list provided in the documents cited above:

- Proof of fee payment to INFARMED
- Annex I (Clinical Trial Application Form) correctly completed and signed by the submitter
- XML File, document obtained from the submission to the EudraCT database
- Protocol and all applicable amendments
- Investigator’s Brochure
- Information on the IMP
- Investigational Medicinal Product Dossier (IMPD)
- Summary of Product Characteristics (SmPC)
- Other documents as stated in the verification list.

To the sites’ IRB and Board of Directors, in addition to all documents already described for observational studies, it is necessary to submit the approval from INFARMED and the favourable opinion from CEIC and the Insurance Policy provided for subject protection.

**Initiation visits**

Again, due to the complexity of clinical trials, the trial initiation visits should take into account the visit to the laboratory and the hospital pharmacy in order to give information about the study protocols. As a result of the involvement of more people and more services, the initiation visit can be broken down into several days in consideration of personal availability to attend such meetings.

During my nine month internship I had the opportunity to observe one clinical trial initiation visit focused on the principal investigator.

**Monitoring visits**

Besides all the activities performed in monitoring visits for observational studies, a few more are added concerning the IMP demands:

- Active search for adverse events not registered in the CRF.
• Ascertain whether the PI took all the appropriate actions to report SAEs.
• Ascertain whether the PI received and acknowledged information such as letters to the investigator, updates to Investigator Brochure, Periodic Safety Reports for Investigators.
• Perform medication accountability.
• Verify that there is enough IMP.
• Verify IMP related records: temperature, reception, delivery and return.

During my internship I followed a monitoring visit to the hospital pharmacy, in which I collaborated in performing IMP accountability, assessing patient compliance, verifying the temperature records and monitoring the logs of the reception, delivery and return of study medication.

Close-out visits

Once again, the close-out visits should encompass activities related to IMP handling, as in the example of the destruction or return to the sponsor of the IMP. Because of the involvement of more site departments, a close-out visit could take more time in order to ensure that all activities in those departments are verified and documented.

Before close-out visits and due to the workload, sometimes visits for query resolution are done, performed after the closure of the CRFs; these only consist in the resolution of discrepant data. These queries are issued by data management but for their resolution it is necessary to involve the CRA, since he represents the bridge between the sponsor or CRO and the site itself.
4. Discussion

In this chapter I intend to critically appraise the internship at KeyPoint, describing exactly what competencies I gained through this experience and highlighting the importance of my academic background. For every experience of on-the-job training, I also want to give a vision of the greatest difficulties I found and how I overcame them.

Monitoring

The fact that the internship provided a great practical experience, instead of following a theoretical approach, has enhanced the acquisition of skills not obtainable in the academic environment. Although there was always an introductory explanation before every task, it was by doing it, and doing it autonomously, that the learning of how things are performed was fostered.

Still, training sessions could have been helpful to better systematise knowledge, and to give a sequential logic to the upcoming tasks; because the projects were already in development, I began working in monitoring visits without a deep knowledge of what happened before this stage - in this case, without knowing about the study submission and study initiation visit procedures.

With this proviso, a point that must be considered is the fact that the practical method gave me a capacity to work with the unexpected; to solve problems, always looking for the best solution. The necessity to be autonomous and to have a problem-solving attitude were skills already acquired during the academic training, but it is only with daily on-the-job activities that these attitudes are matured with the sense of work efficiency.

Concerning the objective of acquiring knowledge in the clinical monitoring area, I must say that it was not totally achieved: as a CRA trainee I have participated in all stages of an observational study; from the initiation and follow-up by phone, to monitoring visits and close-out visits. However, I would like to have had more opportunities to follow a clinical trial, but the company conditions (few clinical trials due to expertise in observational studies) did not provide me with that experience.

Despite this, all the activities performed in the scope of the observational studies allowed me to understand the process of the development of the clinical research, contributing to
training me as a professional with a comprehensive experience in this subset of studies, and it also gave me the foundations of clinical trials, besides the reinforcement of the desire for going even further.

Generally, the adaptation to the theoretical part of each activity was easy, but there were always some minor struggles when executing the tasks appointed, presented here divided per study stage.

**Initial contact with the sites, study presentation and site feasibility:**

This phase is of extreme importance: on one hand it is necessary to interest the investigator enough to participate in the study; on the other hand it is important to evaluate correctly the study team availability and resources. For such a task it’s necessary to have a deep knowledge of the protocol and of the study in general, to better evaluate the necessities, and have a fluid speech to correctly explain the study.

In this phase my interpersonal communication difficulties really stood out, especially when contact with the sites was realised over the phone. In order to overcome this problem initially I would write an agenda with all the topics which needed addressing, and isolated myself in order to better concentrate on the task. Over time, with practice and because it became a routine activity, I no longer needed an agenda, and although I still write it, it now performs only the function of a checklist.

**Study submission:**

As mentioned in the previous chapter, the study submission is a stage that requires careful planning; all the documentation must be prepared, signed and gathered in advance, a task that may require a relatively long time to perform. When submitting to an authority, the applicant must be prepared to answer quickly any requests for additional information by the competent authorities in order to avoid delays. The submission to study sites generally starts after obtaining authorisation from the competent authorities and is a really slow process; a major contributing factor to this is that Portugal seems not to be desirable for the realisation of clinical studies.
In this phase the main struggle is to get an approval fast; a previous knowledge of the site requirements, such as site templates for financial agreements, IRB submission form, etc., and a close follow-up may help in the study submission, but for the submission to authorities, the only solution is to be prepared for the sake of avoiding delays.

I actively participated in the gathering of information to each study site, collaborating with KeyPoint, in pursuance of developing a database with all the information necessary to submit a study.

**Study initiation:**

This is the moment when the investigational team is trained in the study procedures. The main skills necessary are good communication capabilities and a profound knowledge of the study protocol.

In my experience the major difficulties are linked to practical details, such as scheduling a visit with all the investigational team, which is a task that may be problematic due to the time constraints of each study team member and, when it is possible to schedule the visit, it may be difficult to have sufficient time to address all necessary topics while still passing the correct message.

In KeyPoint I had the opportunity to develop a presentation template for study initiation, which I thought would be helpful to standardise the topics that must be covered in this type of visit, maintaining the attractiveness of the presentation to captivate the investigator’s attention.

Personally, I believe that the introduction of information technology can be seen as an ‘enabler’ and the use of smart phones or tablets can really help improve the monitoring performance, resulting in benefits to the productivity, communication and organisation. Although not easy to implement, I consider that this tool should be used with more frequency.

One example related to the stage of study initiation is the electronic agendas, which are useful to invite all study team elements to a meeting and receiving fast responses regarding the availability of each individual.
Study monitoring:

For the realisation of these visits, flexibility and adaptability are necessary, especially when considering the time and the physical conditions needed to conduct the monitoring activities, and it is essential to pay attention to detail, besides having the obligatory good interpersonal skills.

Computerised clinical records are not a widespread reality at every site in Portugal and it is understood that handwritten clinical records can present an arduous task. Also related is the fact that the clinical records are lacking study-related information; sometimes the investigator sees the CRF as the source document, a misconception that does not allow the CRA to confirm the data. The education for investigational practices should be a reality in the training of investigators because sometimes, although they are willing, the investigators lack the practical competencies to conduct a solid, trouble-free research.

Another aspect is the necessity to devote time to the research activities. Almost all investigators accumulate the normal daily work of various studies meaning, in the end, that they are neglecting the less important studies which are, invariably, the observational ones.

As mentioned already in the section regarding the state of the art, it is necessary to implement integrated information systems, to invest in education for clinical research and to review the impact of clinical research on the careers of the investigators.

In my view, there are two ways of reviewing the impact of clinical research on the career of the investigator: create sites only dedicated to investigation, for which investigators with a background in investigation could be contracted; or the hospitals could assign time to clinical research activities, and create proper channels to compensate the investigators for their efforts in participating in the area. A transversal topic to both solutions must be investment in the education in GCPs and clinical research procedures, through promoted courses.

Again during monitoring visits, I found it useful to use my own electronic tool. I developed a simple “yes” or “no” checklist that helped me to focus on what needed to be done during the visit and pre-prepared the site monitoring visit reports, adding valuable information. I realise now that even though the tool wasn’t fully developed, I could have introduced it to
KeyPoint in order to help other Monitors to perform monitoring visits. I understand now that these tools are common practice in other companies and clearly valuable.

Close-out Visit

This is a critical phase that reflects the quality of the monitoring visits. If the site follow-up wasn’t effective, a lot of issues will arise: queries, missing documents and even displeased study teams. It is the type of visit that requires the ability of the investigator to ‘tie up all the loose ends’ or to solve all pending questions. Although I performed a fairly significant number of study close-out visits, as the project came to a premature end, these visits were relatively simple, and there wasn’t any opportunity to follow study close-out visits from other projects.

Related to observational studies and to the activity of the CRA, there were two points not covered during my internship in KeyPoint:

The first was the submission of protocol amendments: due to lack of opportunity, I did not participate or assist in protocol amendment submission. Luckily, I gained this experience from the collaboration in the Clinical Research Office at the University of Aveiro.

The second was the accompaniment of audits or inspections; again, this was due to lack of opportunity. It was of personal interest to observe how an audit to a study site is realised; an experience that I consider helps make the Monitor a better professional.

Beside the experience, which is already an invaluable aid to personal growth, I was able to develop other soft skills:

- Autonomy: after being accompanied on the first visits, I began to do my tasks autonomously, volunteering often to go to visits alone.
- Organisation: by virtue of having five different observational studies to work on, there was the necessity to develop a sense of organisation, and even to use management tools, as simple as a task-list, or more complex, such as integrated agendas.
Time management: this was developed in conjunction with organisation, because there was the necessity to divide my attention between the five projects, and to develop a sense of priority, which in the end is composed of time management.

Interpersonal communication: as a more introverted person, I had initially feared that this area was the wrong one to work in, but the necessity to talk and interact with people as a routine has helped me to develop my interpersonal skills and, in a certain way, to overcome my fear.

“Eye for detail”: the fact that I could repeat the tasks mentioned above, after observing, has helped me to pay more attention to detail in such a way that only a real experience can provide.

Planning: It was necessary to plan visits, which involved anticipating costs, providing logistics for transport, delineating a route, foreseeing the site needs, etc.

I learned also to be adaptable and flexible, because it is possible that the circumstances of a visit can change due to a myriad of constraints, and it is necessary to adapt to the new situations without wasting the visit. I also learned that proactively - anticipating tasks - makes the burden of unexpected events easier to assimilate.

In the end, it is up to the Monitor to accommodate the demands of the sponsor; a difficult task that involves a constant effort to drive the study to a successful end, and one for which soft skill resources are a must in order for a Monitor to succeed.

Other internship activities

In practice, beside the CRA related activities, I had the opportunity to occupy the position of CTA: initiating the studies, contacting the sites to gather documents essential for submissions, actually performing and following up the submissions by contacting IRB and the Management Board secretariat, and by preparing all study-related materials for the observational studies.

The opportunity to participate in data management, medical writing and in statistics, even for brief periods of time, gave me a good perception of how other activities contribute to the overall outcome of a project.
It was in the area of Medical Writing that I had a training session focused on how to develop systematic revisions. I considered the training very helpful, especially because I was invited to participate in the refinement of a systematic review.

After the project was concluded, the Medical Writer technician suggested the implementation of Standard Operating Procedure to help in the construction of scientific articles, in which would be indicated what scales should be used for each type of article, (e.g. PEDro scale for systematic reviews, STROBE scale for the report of Observational Studies, etc.), alongside what topics should be covered in each chapter of the article. I helped in the systematisation of the content of articles suggested as examples by the scale developer teams. Due to professional reasons, the colleague had to leave the company, and the project was dropped. Retrospectively, I understand how useful it could have been for my own personal growth if I had continued the project; however, due to lack of knowledge, it was not possible for me to carry on the project.

In data management it is clear that there is an added value of the electronic CRFs when compared with the paper CRFs, because of the supplemental tools that a web-based application can offer: alerts, audit trail, query issue, data export for statistical and management tools, etc.

I also agree with the data manager’s point of view that data can really help a clinical study Monitor to better monitor the data on-site and to better correct and present information. An actual example is the correct use of the buzzwords “unknown”, “not performed” or “not applicable”, instead of leaving the field blank; the simple information of “not performed” has a precise meaning, whereas a blank field could correspond to a forgotten answer.

**The CRO’s role**

At the end of the internship it was possible to better understand the position of a CRO in the pharmaceutical area: a CRO is a person or an organisation (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor’s trial-related duties and functions. Organisations that contract CROs do so to acquire specific expertise without hiring permanent staff.
Pharmaceutical companies are faced with the pressure of the R&D cost rise, and as a result some pharmaceutical companies have downsized, out-licensed non-major products, merged, developed their over-the-counter market and some have simply given up clinical research altogether. There was a clear necessity to reduce the cost of bringing a medicine to the market and as a result CROs were created to fill this demand. Due to the different competencies of the pharmaceutical companies, offering specific expertise without the necessity of hiring permanent staff, CROs managed to grow and to develop a new research niche.

They offer services such as project management, database design & build, data entry & validation, clinical trial data management, medicine and disease coding, quality and metric reporting, statistical analysis plans and reports, validation programming, safety and efficacy summaries and the final study report.

**Importance of the academic background**

My Bachelor’s degree in Biomedical Sciences has given me the foundations in clinical sciences and introduced me to the medicine development phases. The Master’s course in Pharmaceutical Medicine, as a truly comprehensive course covering in depth the entire life-cycle of a medicine, gave me the knowledge to achieve professional autonomy faster. My academic background ultimately has given me the support to make an informed decision as to where to begin my professional career, and to assume a rewarding position in the activities in which I participate.

In all the areas in which I had the opportunity to participate during my internship, the impact of the Master’s course was obvious, preparing me to perform the proposed tasks with a solid background due to the devoted units of:

- Medical Writing, where we were required to learn how to produce scientific documents effectively and efficiently;
- Ethics, where the Helsinki declaration was addressed, along with the GCPs and all other applicable regulations for the protection of subjects’ rights and well-being;
- Data Managements and Statistics, in which were laid down the basic principles for data monitoring, and for data management;
- Regulatory Affairs, where knowledge about study submission procedures and applicable regulations was acquired.

Other opportunities offered during the Master’s course that I consider relevant to my education was the opportunity to take on an internship as site study coordinator, which allowed me to understand the dynamics behind an investigational team, and to collaborate in the Clinical Research Office, developing a project from scratch, which gave us a preview of the internship.
5. Conclusion

At the end of this internship I believe that I chose the correct area; one that makes me strive to do my best, and that propels me to develop a solid professional career. The KeyPoint Group was a good place to begin this path, and it has allowed me to grow as a professional, keeping me surrounded by help, good advice and a friendly environment.

Although I understand that I still have much to learn and much to improve upon, I believe that I have acquired the knowledge and the skills to be a Clinical Research Associate.

The fact that I was in a small CRO was undoubtedly the perfect way to gain experience in other areas, even making my own contributions to some of them, and it was fundamental to understanding the working processes of a CRO and their importance in the pharmaceutical area. Although perhaps in a larger company I could have received more substantial training in clinical research, maybe even participating actively in clinical trials, the experience in KeyPoint was more comprehensive and more “personal”.

My appreciation also to the Master’s course in Pharmaceutical Medicine, which has influenced me deeply, and which makes me proud to have had the opportunity to participate in it. The multidisciplinary approach focused upon, in the clinical research, was revealed to be the appropriate and missing piece to addressing the lack of specialised education in the area and as a true, useful asset.

This experience has allowed me to understand what the field of action is and what is expected from the clinical studies Monitor, as well as how clinical trials ultimately mean access to new and innovative medicines that can make a difference to the future of each patient. I also realised that it is necessary to analyse the weaknesses of our country and make the necessary efforts to make Portugal a competitive and desired country in which to develop clinical research.
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