Universidade de Aveiro Secção Autónoma de Ciências da Saúde
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DIANA CRISTINA BRITO OLIVEIRA

MONITORIZAÇÃO DE ENSAIOS CLÍNICOS – ESTÁGIO NUMA *FULL SERVICE CRO*

DOCUMENTO PROVISÓRIO

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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 do Doutor Wim Amed Paul Roosens, Diretor Médico da Datamedica, Serviços e Consultoria em Bioestatística, Lda e da Professora Adjunta Maria Joana da Costa Gomes da Silva da Escola Superior de Saúde da Universidade de Aveiro

Dedico este trabalho à minha família e amigos pelo incansável apoio prestado e pelos momentos de alegria que me proporcionam.

"Don't judge each day by the harvest you reap but by the seeds that you plant"
- Robert Louis Stevenson

o júri

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agradecimentos

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À minha irmã, por todas as gargalhadas e momentos felizes.

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palavras-chave

Estágio, CRO, Ensaios Clínicos, Monitorização, Biomedicina Farmacêutica, Datamedica.

resumo

O presente relatório destina-se a descrever a minha experiência enquanto estagiária em Datamedica, Serviços e Consultoria em Bioestatística, Lda, uma Contract Research Organisation (CRO). Este estágio teve como objetivo colocar em prática todo o conhecimento adquirido enquanto aluna do Mestrado de Biomedicina Farmacêutica, dado que os profissionais desta competência estão aptos a realizar atividades que envolvem todo o ciclo de vida do medicamento.

Esta experiência focou diversas atividades dentro da empresa, como Farmacovigilância, Medical Writing e Gestão de Qualidade, de modo a perceber a dinâmica e o papel de uma CRO num meio tão competitivo quanto a indústria farmacêutica. No entanto, a minha experiência curricular de 9 meses centrou-se maioritariamente em monitorização de ensaios clínicos, onde tive oportunidade de desenvolver as competências concernentes à condução de ensaios clínicos. Durante este período de estágio participei em dois estudos observacionais e oito ensaios clínicos, no papel de monitora. Desta forma, pude perceber a importância da monitorização de modo a garantir tanto a segurança, bem-estar e os direitos dos participantes, como a fiabilidade dos dados que são recolhidos.

keywords

Internship, CRO, Clinical Trials, Monitoring, Pharmaceutical Medicine, Datamedica.

abstract

This report intends to describe my internship experience at Datamedica, Serviços e Consultoria em Bioestatística, Lda, a Contract Research Organisation (CRO). This internship had the objective of applying the knowledge acquired as a Master Student of Pharmaceutical Medicine, since Pharmaceutical Medicine professionals are capable of performing activities in all the medicines' life cycle.

This experience focused on different activities, such as Pharmacovigilance, Medical Writing and Quality Management, in order to understand the role and dynamics of a CRO in a competitive environment such as the pharmaceutical industry. However, my curricular 9-month experience was primarily focused on clinical trial monitoring, where I got the chance to develop the know-how related to clinical trial conduction. During the internship period, I was able to participate in two observational studies and eight clinical trials, as a study monitor. This way, I could understand the importance of monitoring so that participants' safety, well-being and rights are guaranteed, as well as the reliability of gathered data.

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Abbreviations List

AE – Adverse Event

CEIC - Comissão de Ética para a Investigação Clínica

CIAV – Centro de Informação Anti-Venenos

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

DCF – Data Clarification Form

DLP – Data Lock Point

e.g. - exempli gratia

EC – European Commission

eCRF – Electronic Case Report Form

EMA – European Medicines Agency

Eudravigilance - European Union Drug Regulating Authorities Pharmacovigilance

EURD list - List of European Union reference dates and frequency of submission of Periodic Safety Update Reports

FDA – Food and Drug Administration

GCP - Good Clinical Practices

GMP – Good Manufacturing Pratices

GVP – Good Pharmacovigilance Pratices

IB – Investigators BrochureICF – Informed Consent Form

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

ICH- GCP - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practices

ICSR – Individual Case Safety Report

IEC – Institutional Ethics Committee

IF – Investigator File

IMP - Investigational Medicinal Product

IMPD – Investigational Medicinal Product Dossier

INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P

IRB – Institutional Review Board

MA –Marketing Authorisation

MAH – Marketing Authorization Holder

MedDRA - Medical Dictionary for Regulatory Activities

PI – Principal Investigator

PSUR – Periodic Safety Update Report

R&D – Research and Development

SAE – Serious Adverse Event

SDV – Source Data Verification

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

TMF – Trial Master File

US – United States

US CFR – United States Code of Federal Regulations

USA – United States of America

1. Introduction

This report intends to describe a curricular internship that took place from September 2012 to June 2013 in the scope of the Master Course in Pharmaceutical Medicine of University of Aveiro. The host institution for this internship was Datamedica, Consultoria e Serviços em Bioestatística, Lda., a full service Contract Research Organization (CRO), herein referred to as Datamedica, Lda.

The main focus of this internship was clinical trial monitoring. The development of activities in several areas was important to understand how every element works in an integrated manner to achieve success in a project.

The training focused on two major components:

- Clinical Trial monitoring activities;
- Contact with, observation and experimentation in other clinical trial-related areas (Pharmacovigilance, Medical Writing and Quality Management).

This document describes the activities developed over the 9-month internship at Datamedica, Lda and for that purpose it is organized in the following chapters:

- **Introduction**: in this chapter are explored the objectives proposed to be achieved during the internship. It also provides an insight on the host institution where the internship occurred;
- **State of the art:** in this chapter is provided an overview of clinical trials and observational studies with emphasis on definitions and current legislation. The monitor role is also explored;
- **On-the-job Training**: in this chapter the activities that were developed during the internship are described. The activities are divided in two sections, one concerning the generic training which includes activities in different areas and the second describing the specific training which consists in clinical trial monitoring activities;
- **Discussion:** this chapter provides a reflection on the skills and competencies developed throughout the internship and how the difficulties encountered served as a mean through which professional growth was achieved. The contribution of the trainee's academic formation is also weighted.
- **Conclusions**, where a reflection of what was gained from this experience is presented.

1.1. Training Objectives

My training objectives were established in such a way that they have given me the possibility to make the most from each and every experience. As so, I established the following objectives to be accomplished during my internship:

- Primary objectives:
    - To gain expertise in the area of clinical monitoring and clinical trial conduction, comprising all its requirements, deliverables and specificities, always having in mind the Good Clinical Practices (GCP) and all regulatory applicable requirements and guidelines;
    - To obtain a first professional experience, to grow as a clinical research professional, and to increase soft skills via personal development which would be a facilitator in the context of my professional area.
- Secondary Objectives:
    - To understand how a small-size CRO operates and how it establishes business relationships with pharmaceutical companies;
    - To gain knowledge in several areas that are complementary to clinical monitoring activities and to understand the dynamics behind these processes in a context of a full service CRO's activities.

1.2. Vision of the host institution

Datamedica, Serviços em Consultoria e Bioestatística, Lda was established in 1996, with headquarters in Lisbon, initiating its activity in the field of Biostatistics. As time went by, the company expanded its services into other areas, in order to meet clients' needs and to follow the scientific and technological advances. In 1997, the monitoring services began, in 1998 the epidemiology services were established, in 1999 the medical informatics, in 2000 the pharmacoeconomic services and finally in 2001 the pharmacoepidemiology services (1).

Datamedica is a Portuguese small size full-service CRO aiming to achieve recognition by others through the provided services. Datamedica's clients are pharmaceutical companies, universities, investigators and organizations with interests in clinical research. Among its clients are about 30 pharmaceutical companies, 19 of which are in the top 20 of major companies in Portugal (1). At an international level, Datamedica has been working with multiple CROs, which has allowed bringing to the country clinical trials of international scope (1).

The company has experience in therapeutic areas such as oncology, cardiovascular diseases, endocrinology, rheumatology and neurological diseases (2). More recently, Datamedica has developed business in the area of hospital management, in order to reach and help developing a healthcare network in underdeveloped countries, in the African continent.

The company is organized into departments, working together in the different projects. Datamedica is constituted by a multidisciplinary team and all collaborators are submitted to a period of training before becoming autonomous. Team work is a key value in the company. The company structure is shown in Figure 1.

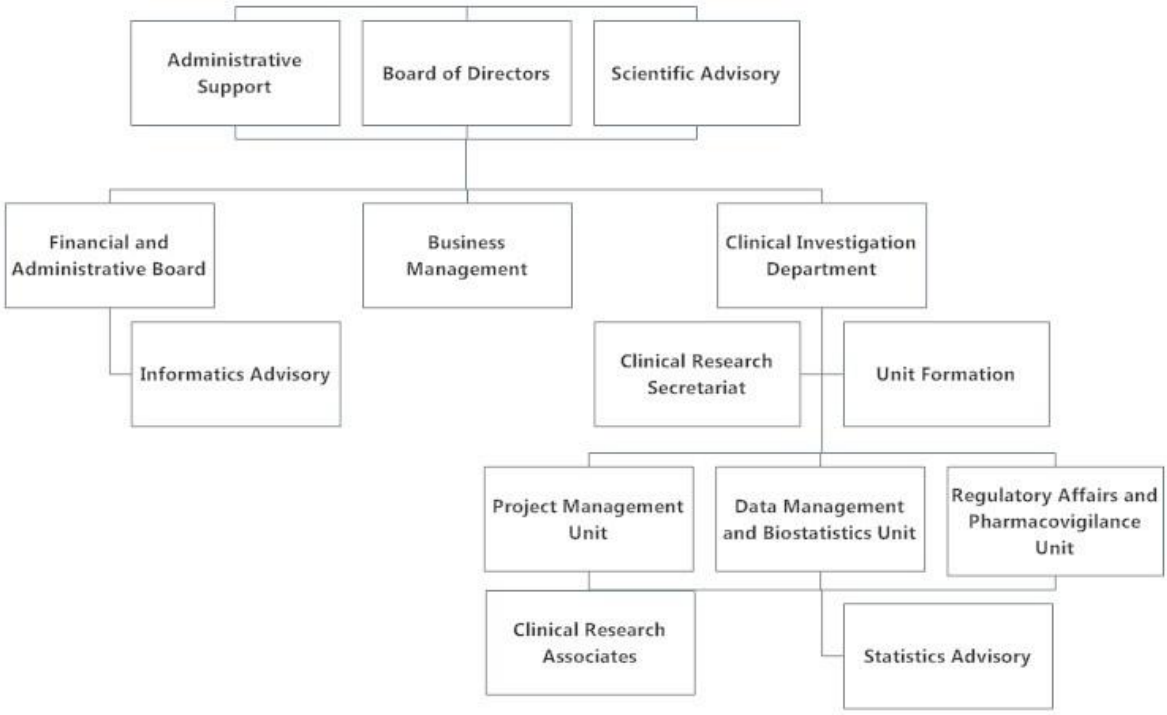

Figure 1 - Structural Organization of Datamedica, Lda. (3)

During my internship I have been working in the Clinical Investigation Department, more specifically in the Project Management Unit, as a monitor of clinical trials. In the Project Management Unit, there are four collaborators: a Medical Director, who coordenates all clinical research activities and three Clinical Research Associates (CRAs), including myself. Ocasionally, the person responsible for Pharmacovigilance collaborates with this Unit.

Currently, Datamedica offers solutions and partnerships in several areas of clinical research. These areas include Clinical Trial Monitoring, Biostatistics, Epidemiology, Pharmacoepidemiology, Pharmacoeconomy, Bioinformatics, Medical Writing and Meta-analysis (2).

The company aims to provide services in a range of activities protocol design, Case Report Form (CRF) design, submission to competent authorities, monitoring site and study progress, report to international teams and preparing clinical study reports (4).

In the scope of Pharmacovigilance, the company provides services related to daily database research, elaboration of Periodic Safety Update Reports (PSUR) and adverse reactions reporting to the competent authorities (4).

2. State of the Art

Clinical Research can be defined as a set of activities involving human subjects undertaken in order to gain knowledge about a specific hypothesis (5). The hypothesis under study can be related to human disease conditions, human behaviors, effects of therapies, interventions and diagnostic methods (5). Observational studies and clinical trials are the two main types of clinical research approaches. According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practices (ICH-GCP), it is required for the sponsor to monitor the trial in order to guarantee the safety and well-being of the trial subjects, as well as the reliability of the data obtained (6). Thus, one key element in clinical research is the CRA or monitor, who oversees this process and guarantees that all requirements are fulfilled. For observational studies, this is not a mandatory requirement but it is recommendable for the proper conduction of the study.

2.1. Observational Studies

Observational studies are a particular type of clinical research study in which the subjects are observed and there is no active intervention, e.g. no treatment is given or no alteration to the current treatment is made.

These studies often measure certain outcomes or intend to establish hypothesis (7). Inferences may be established through this type of studies related to the outcomes of a certain exposure or intervention. In observational studies there is no change in the subjects' usual routine, since the objective is only to observe the subjects without any type of intervention that may affect the outcome (7).

According to the Good Pharmacovigilance Practices (GVP) reference, a trial is considered observational or non-interventional if the following conditions are cumulatively verified (8):

a) the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization;
b) 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;

c) no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

According to Portuguese Law 46/2004, of 19th of August (7), observational studies are studies within the scope of the marketing authorization foreseen conditions, in which the conditions to be verified comply with the ones present in the GVP.

Non-interventional studies are classified according to the methodological approach used. Generally these types of studies involve searching in databases or reviewing health records (retrospective design). Nevertheless, they can also involve primary data collection from routine clinical appointments, in this case assuming a prospective design (8).

The three usual designs for observational studies are cross-sectional, cohort and case-control. Each one of these study types has particularities and depending on the study objectives, the more suitable one should be chosen (9).

Cross-sectional studies are described as a snapshot of a single time point of a defined group of individuals. These studies assess the exposure and the outcome simultaneously and are generally used to estimate the prevalence of a condition. These studies are suitable when the study of a hypothesis is needed, since they require less resources, fewer time and allow studying a diverse stratum of the population (9).

Cohort studies (also called longitudinal studies) are used for providing data from a specific population over time. These studies can be either prospective or retrospective (9). Cohort studies allow following individuals exposed and not exposed to a certain factor to see if they develop a certain outcome. These factors can be identified through cross-sectional studies and then explored in cohort studies. This way, the natural course of a disease or condition can be explored and incidence rates and relative risks obtained.
It is feasible to choose a cohort design when the following conditions are met (9):

- There is evidence of relation between a factor and an outcome;
- The time interval between the exposure to the factor and the development of the condition is not so long that it can cause loss of data to follow-up;

- The sample size is acceptable in order to achieve statistical significance, meaning that the condition studied is not rare.

Cohort studies are expensive and time-consuming. Nevertheless, they can provide information that otherwise would not be gathered (9).

Finally, case-control studies, unlike cohort studies, are suitable for studying rare diseases or conditions, since the start point is the outcome and only after the cause factor is analyzed. In these studies, the subjects that have the specific outcome are termed "cases", while the subjects who do not have the outcome are termed "controls", hence the terminology "case-control" study. These two groups are compared in what regards their background of exposure to the factor being studied (9,10).

This type of design is suitable when (9, 10):

- The condition under study is of rare occurrence;
- There is proof of exposure to the study factor in the past.

In Portugal, a specific regulation for observational studies does not exist. The conduction of these studies requires the authorization of Comissão Nacional de Proteção de Dados (CNPD) and the Institutional Board of each study center. The requirements for this type of submissions depend on the individual requirements of each study center.

2.2. Clinical Trials

2.2.1. Classification

A clinical trial is defined by the ICH-GCP 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." (6).

Clinical trials are traditionally classified as Phase I to Phase IV trials depending on the study objectives.

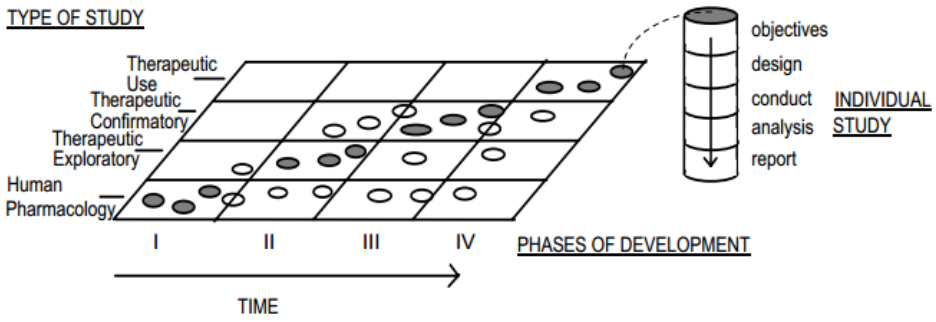

Figure 2 - Correlation between development phases and types of clinical studies (10).

Phase I trials are generally human pharmacology studies, also called first-in-human (FIH) trials. These studies aim to explore the safety (including side effects), tolerability and safe dosage range of the investigational product's administration in humans. Human Pharmacology studies are generally conducted in a small group of healthy volunteers, except when it is not considered ethical to administer a drug in healthy subjects due to its potential toxicity, as in the case of cytotoxic drugs (10).

Phase II trials are therapeutic exploratory studies aiming to explore therapeutic efficacy in patients. These studies are important to determine safe doses and regimens for the later development; and are generally conducted in a larger relatively homogeneous group of patients, with restrictive criteria (10).

Phase III trials aim to demonstrate the therapeutic benefit of the investigational product and are denominated therapeutic confirmatory. These studies are the foundation for marketing approval, establishing the safety profile of the drug and the dose-response relationship, through the collection of data from a large number of subjects (10).

Phase IV trials are called post-authorization trials, since they are performed after the drug is on the market. These are studies of therapeutic use, since they allow refining the understanding of the benefit-risk relationship and the dosing recommendations. In this way, safety and efficacy data related to long-term use can be gathered and less common side effects can be identified. They are important to optimize the drug use or regimen (10).

The traditional definition of clinical trials into Phase I to Phase IV clinical trials does no longer stands truthful, since it implicitly transmits that the trials are sequential in time, which currently does not correspond to what actually happens (10).

2.2.2. International and National Legislation

The pharmaceutical industry is one of the most regulated industries of the globe, assuring in this way the quality of the provided services. Clinical trials are a highly regulated activity as well, since there are many aspects at stake, such as subject's rights and wellbeing and the reliability of the results obtained.

When implementing and conducting a clinical trial, there are many recommendations and guidelines that have to be followed alongside with rules and regulations.

Each country has its specific rules and regulations concerning clinical trials, however these are generally an adaptation of more global recommendations, such as ICH or European Commission (EC) recommendations. Furthermore, considering where the study will be conducted or where the results will be submitted, it must be taken into account the United States (US) Code Federal Regulations (CFR), which is specific for United States of America (USA). This Code regulates clinical trials in the USA, particularly title 21 (21 CFR) that lays down a set of rules from the FDA. For new investigational drugs, the rules laid down by title 21 CFR also regulate the trials conducted outside USA (11).

In Europe there are several directives and recommendations from the EC that have to be followed alongside with the guidelines from the ICH.

One of the most important guidelines to be followed is without doubt ICH-GCP, which is "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects". (11)

Also, all clinical investigation must comply with the Declaration of Helsinki, which establishes the ethical principles for medical research involving human subjects (12).

To conduct a clinical trial in Portugal, there is the need to have in mind the following regulations and recommendations:

European Commission Directives (13):

Directive 2001/20/EC, of the European Parliament and of the Council, of April 4th – attempts to provide a common legal framework for all Member States in what concerns the application of good clinical practices in the conduction of clinical trials. This Directive was

transposed into the national law of each member state. In Portugal, the transposition of this directive is on Law 46/2004, of August 19th (7).

Directive 2001/83/EC of November 6th – Establishes a community regulatory framework in what regards the medicines for human use.

Directive 2003/94/EC of October 8th – Establishes the principles and guidelines on Good Manufacturing Practices (GMP) of medicines for human use and investigational medicines for human use.

Directive 2005/28/EC, of April 8th – Establishes the principles and detailed guidelines on Good Clinical Practices (GCP) for Investigational Medicinal Products (IMPs), as well as the mandatory requirements for the manufacturing and importation of those products. This Directive was transposed into Portuguese law through Decree-Law nr. 102/2007, of April 2nd.

ICH guidelines: provide orientation on several issues regarding pharmaceutical product registration, intending harmonization of key aspects such as safety, quality and efficacy.

EC **Guidelines:** provide guidance on aspects such as clinical trial application, monitoring and pharmacovigilance, quality of the product, inspections and legislation.

National Legislation:

Law nr. 46/2004, of August 19th – Establishes the legal framework for the conduction of clinical trials using medicines for human use.

Decree-Law nr. 176/2006, of August 30th – Medicinal Product Statute.

Decree-Law nr. 102/2007, of April 2nd – Establishes the principles and guidelines on GCPs in what concerns investigational medicinal products for human use, as well as the requirements for manufacturing and importation of those products.

Law nr. 67/98, of October 26th – Establishes the rules for the protection of personal data. This law transposes the Directive 95/46/CE, of October 24th, concerning the protection of personal data of individual subjects.

2.2.3. Clinical Trials in Portugal

In Portugal, to conduct a clinical trial it is necessary to obtain approval or favorable opinion from three different entities (7) (14):

1) the National Competent Authority (Autoridade Nacional do Medicamento e Produtos de Saúde I.P. - INFARMED)
2) the Independent Ethics Committee (Comissão de Ética para a Investigação Clínica - CEIC) and
3) Comissão Nacional de Proteção de Dados (CNPD).

The major pharmaceutical companies are disinvesting in attributing clinical trials to Portugal and a dislocation of these activities to Eastern Europe countries and Asia has been observed. This item has been largely covered by the different media (15). GlaxoSmithKline was one of the companies that have given up performing clinical studies in Portugal about 3 years ago. More recently, Eli Lily has closed its research unit in Portugal. The statistical data shows that the number of clinical trials performed in Portugal has stagnated, when it should be increasing since now more clinical studies are needed in order to launch a medicine in the market (15, 17).

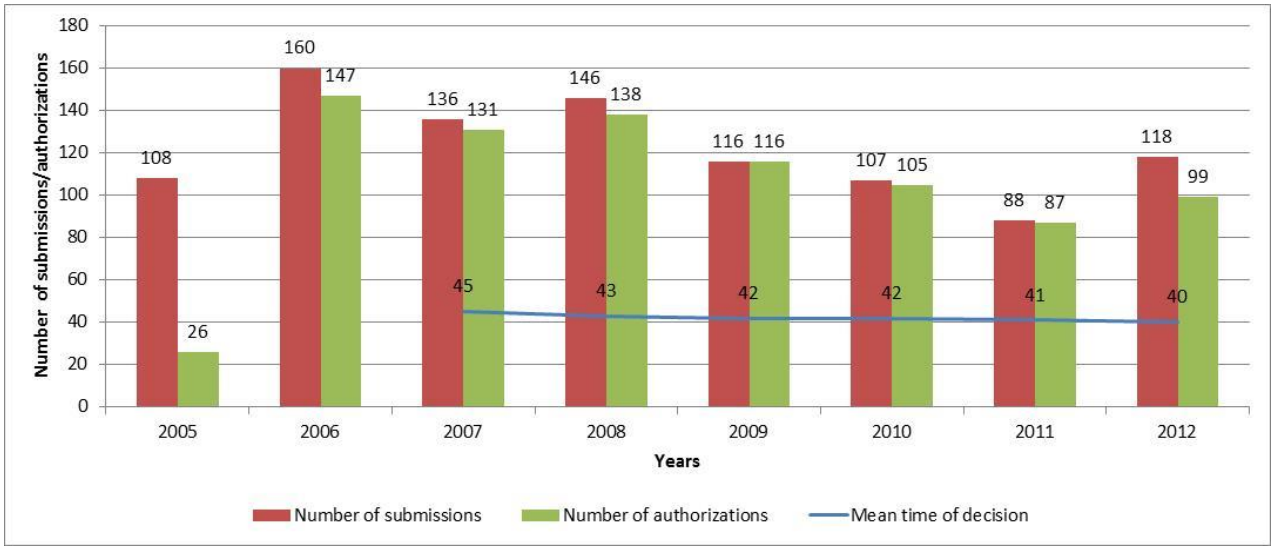

Figure 3 - Number of Clinical Trial Applications submitted to INFARMED (2005-2012) and average time of decision (in days) [adapted from (16)].

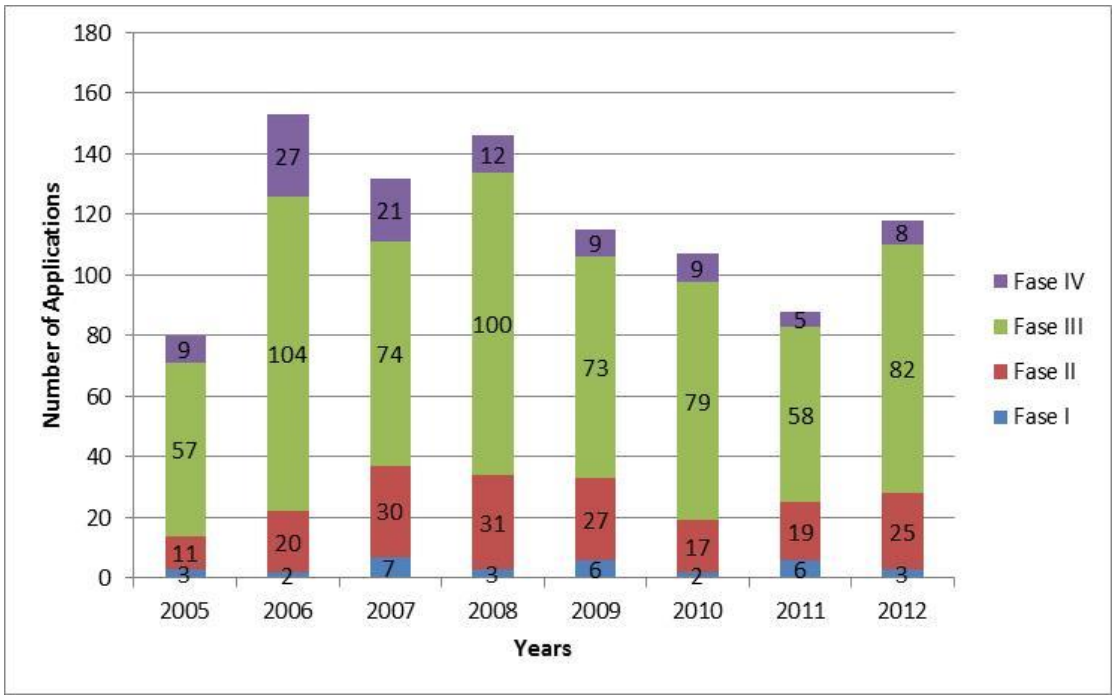

Figure 4 – Number of Trials per Clinical Development Phase and year Submitted to INFARMED (2005-2012) [adapted from (16)].

On the other hand, companies like Boehringer Ingelheim consider Portugal a key country in which to implement phase II to IV clinical trials. Pfizer has approximately 30 clinical trials ongoing in Portugal in areas like oncology, neurology, cardiology and others, but has closed down its clinical trial unit in Portugal in November 2012.

According to an estimate from the pharmaceutical industry (APIFARMA), Portugal loses about 135 millions of euros per year due to the fact that the number of clinical trials hospitals conduct represent less than a half of their capacity. This return on investment could be easily used to invest in more clinical trials or to help financing the proper hospitals, e.g. hospital equipment (2).

For example, in the oncology area there exists a problem regarding the participation in clinical trials. Some people defend that most oncologic patients should be given the opportunity to enter a clinical trial, which does not happen. In countries like United Kingdom and USA, only 10% of the oncologic patients participate in trials, and in Portugal the scenario is even worse since only about 2% of those patients have this opportunity (17). However, in Portugal the oncology area is by far the most well represented therapeutic area, since 30% of all clinical trials are in this area. For example, Portugal is a first choice country to perform lung cancer clinical trials (18).

Data from INFARMED confirms that the number of clinical trials conducted between 2006 and 2009 has decreased about 21%. In 2008, 70 million euros were invested in Portugal in clinical trials, whereas in 2009 this investment decreased to 58,8 million, in a total of 147 clinical trials. In 2012, 99 Clinical Trial Applications were evaluated and submitted. The mean evaluation time was 40 days and all processes were concluded within legal deadline (19).

Conducting clinical trials in Portugal has its advantages and disadvantages. The advantages include the fact that Portugal detains several universities and central hospitals capable of conducting clinical research, since their staff is qualified and experienced. Most investigators have enormous experience in conducting clinical studies and have an excellent mastery of the English language, which is essential at this point. Portugal fulfills the legal requirements imposed by the European Medicines Agency (EMA) and as such conducting a clinical trial in this country is a guarantee of quality which is supervised by INFARMED and CEIC. The possibility of testing a medicine in the Portuguese population, which is a population characterized by ethnic variety and huge potential of study subjects, is also attractive. To test an investigational product in several populations is an objective of the sponsor in order to eliminate, as much as possible, the multiplicity of factors existing between countries. Furthermore, the national scientific production has increased and it has achieved better quality and better organization. The common taxpayer and healthcare

professionals are interested in implementing measures that have the potential to improve healthcare.

Unfortunately, Portugal has also characteristics that are disadvantageous to potential sponsors when there is an opportunity for conducting a clinical trial. Portuguese hospitals take a long period of time to approve a study and consequently to start the study procedures in patients. In some hospitals administrative procedures can take about 6 months, even after the study has already been approved by the regulatory authorities (i.e. INFARMED and CEIC). As a consequence, the sponsors prefer European countries where the approval is faster (e.g. Eastern Europe). In what regards to the competent authority, INFARMED claims that assessments are being granted within 40 days of the submission, therefore respecting the 60 days defined by law (19).

CEIC average time for assessment is 66 days, but most of the trials are assessed within 60 days. One particularity that can delay the procedure is the fact that the clock stops whenever there is a request to the applicant to submit additional information or clarifications to the competent authorities. The time spend for regulatory authorities' approval plus the time that sponsors need to wait to get hospital's approval is too much for a company wishing to see its product on the market and this is leading to investment loss. As a consequence of all these delays, the process can take for about 1 year to get the study started and this can mean that the study is starting in Portugal when it is already finishing in another country. In the view of the pharmaceutical industry this is money lost.

Another particularity is that to implement a clinical trial in Portugal the approval of three entities is needed: INFARMED, the national competent authority, CEIC, the national health committee and CNPD, a commission which aims to protect the privacy of the study subjects.

As Portugal has a chronic delay in assessing and approving clinical trials, a negative image of the country in this field is created in the foreign. So, sponsors do not choose Portugal because the process is slower and more expensive than other countries like Ukraine and Romania. Another disadvantage is the fact that Portugal is lacking organization at a national level, hospital level and hospital's internal infrastructures, and there is also lack of political will in promoting Research & Development (R&D). The communication between investigators is poor and there is lack of organized centers/sites, which would be attractive to sponsors if they had the opportunity to have five or six well organized sites in Portugal

with appropriate infrastructures and simplified administration to safely conduct a clinical trial at excellence level. At the hospital level, it is recognized that hospitals are below their actual capacity to perform clinical trials, since in reality they could perform the double or the triple of the number of clinical trials they actually perform.

As the timelines for approval are many times delayed, the time for inclusion of patients in the study is shortened which leads to less patients enrolled in each clinical trial and which is also a major disadvantage that can lead to the failure in the country's commitments/ objectives established by the sponsors.

Health services do not receive incentives to collaborate in the activities involving clinical trials, hence they do not feel the need to set the bar high.

In order to eliminate the tendency for the decreasing clinical trials' participation in Portugal, there are several aspects that have to be taken into account by the responsible bodies (20):

- It is of extreme importance that Portugal establishes methods for networking and for sharing information between all healthcare professionals and other players involved in R&D;
- The infrastructures for the conduction of clinical trials need to be improved, otherwise pharmaceutical companies will have to supply the necessary essential equipment, which can be a factor of exclusion;
- Clinical trials are of great value for the Portuguese population since they allow the Portuguese clinical staff to develop experience in clinical research, at international level and because they permit to gather data from the Portuguese population concerning a particular medication;
- It is fundamental the development of incentive mechanisms for clinical research, mostly because this is a mean through which many patients have access to innovative therapies;
- It would be of great value to optimize the assessment/approval timelines for INFARMED, CEIC, CNPD and particularly hospital's administrations, in order to try to match the approval timelines in other European countries;
- It is necessary to establish goals and objectives, to recognize the value of clinical investigation activities in what regards the evaluation indicators and the funding of

those activities, specially to redistribute the promotion of investigation support programs using public funds;

- Measures that could simplify the administrative processes should be implemented, such as, developing a structure capable of coordinating all national clinical investigation;
- It should be instituted a national strategy to support clinical investigation;
- Pilot-centers for the conduction of clinical trials should be created in Hospital Units that are prepared for such.

2.3. The role of the monitor in Clinical Research

Monitoring of a clinical trial is defined by ICH-GCP as "the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"(6).

As so, the monitor has a crucial role in the proper conduction of a clinical trial, as well as several responsibilities. The monitor needs to ensure that, above all aspects, the rights and safety of the subjects are guaranteed. Besides, the monitor also assures that the clinical trial data are complete, accurate and supportable by source documents (6).

Monitors are persons adequately trained and appointed by the sponsor, and should have the clinical and/or scientific knowledge in order to monitor the trial appropriately. Monitors should also be acquainted with the investigational product(s), the protocol, the information provided to trial subjects (e.g. informed consent form, ICF), the sponsor's SOPs, GCPs and all applicable regulatory requirements (6).

According to ICH-GCP, the trial monitor has several responsibilities and tasks to perform at the trial site and/or for the trial in general that should be carried out in accordance with the sponsor's requirements (6):

- Constitute the principal mean of communication between the sponsor and the investigator and trial staff;
- Assure that the investigator possesses adequate qualification, training and resources;

- Assure that investigator’s resources remain adequate throughout the trial period and that facilities (e.g. laboratories, equipment, and staff) are satisfactory to safely and properly conduct the trial;
- Ensure that the investigator complies with the approved protocol and all approved protocol amendment(s);
- Verify if every trial subject has given his/her informed consent before initiating any trial procedure;
- Ensure that the investigator receives all trial-related documentation, the current Investigator's Brochure, and all trial supplies needed to conduct the trial properly;
- Ensure that the investigator and the investigator's trial staff are adequately trained on trial procedures;
- Verify if the investigator and the trial staff are performing all delegated trial functions;
- Confirm the eligibility of the trial subjects enrolled by the investigator;
- Report the rate of recruitment, including screen failures;
- Perform source data verification, ensuring that source documents and other trial records are accurate, complete, kept up-to-date and maintained;
- Ensure that the investigator provides all necessary documentation, such as reports, notifications, applications, and submissions, and that these documents are accurate, complete, legible, dated, delivered in a timely manner and identify the trial to which they refer to;
- Check the CRF in several aspects, in what regards accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. Most specifically verify that (6):
    - The protocol required data are accurately reported in the CRFs and match the data stated in the source documents.
    - Any dose and/or therapy alteration are well documented for each of the trial subject.
    - Adverse events (AE), concomitant medication and disease history are reported.
    - All withdrawals and dropouts occurring during the trial are reported and justified.
- Check the CRF for entry errors, omissions, or illegibility and assure that appropriate corrections are made by the investigator or trial staff;

- Determine if all AEs are appropriately reported within the time periods required by GCP, or established per protocol, or according to sponsor's SOPs, and other applicable regulatory requirement(s);
- Verify if the essential study documents are being properly archived;
- Communicate deviations from the protocol, SOPs, GCP, and applicable regulatory requirements.

The monitor also has responsibilities in what regards controlling investigational product and that includes verifying the following (6):

- If storage times and storage conditions are reasonable and as required per protocol or other recommendations;
- If the amount of supplies is sufficient;
- To control to whom the investigational product is being supplied, guaranteeing that only enrolled subjects receive the investigational product;
- If instructions have been provided to subjects on how to use, handle, store and return the investigational product;
- That appropriate and controlled record is maintained concerning the receipt, use and return of the investigational product;
- That the way of disposal of unused investigational product at the site is according to the applicable regulatory requirement(s) and the sponsor's SOPs.

3. On-the-job training

On-the-job training comprised a multidisciplinary experience that included performing tasks in different areas. This training was divided in two parts: generic and specific training. All the tasks performed were always supervised and a prior training was required before becoming autonomous.

The activities in the different areas occurred on demand in parallel with study monitoring.

Figure 5 – Chronological distribution of the activities developed during the internship.

3.1. Generic Training

During my internship at Datamedica I had the opportunity to learn and to explore different areas related to the activities developed by the company for the pharmaceutical industry. To develop experience in these areas was a predefined objective of my internship so that I could gain know-how and understand the dynamics behind the activities that are complementary to clinical monitoring.

One of the areas in which I participated was Pharmacovigilance. The activities developed in the field of Pharmacovigilance were preparation of Periodic Safety Update Reports (PSURs), weekly bibliographical research and adverse reaction reporting to the regulatory authorities. I also had the opportunity to experience some other activities such as Medical Writing, involving the development of protocol synopsis and study protocol and Quality Management, which involved the update of the Quality System from the company.

It is important to state that the first task when entering the company was to read and understand all company's SOPs, so that I got integrated in all processes and procedures of the company for all different areas before performing any tasks.

3.1.1. Pharmacovigilance

Pharmacovigilance is a vital activity in a medicine's life cycle. Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (21).

The monitoring of a drug is a continuous process that should be guaranteed by the Marketing Authorization Holder (MAH). The Pharmacovigilance activities can be subcontracted to a CRO who acts as MAH representative as long as there is constant communication of safety concerns between MAH, CRO and competent authorities.

In the Pharmacovigilance area there are several activities performed in the company that I could experience. When I arrived at the company, my first experience was in this area. I had a training session with the Pharmacovigilance Assistant concerning the procedures and the tasks that were daily performed. This training session abridged the daily and weekly database research and PSUR preparation.

In order to keep the company procedures up-to-date, an extensive reading of the new pharmacovigilance legislation and guidelines for GVPs was necessary.

Besides performing the usual tasks, I had the opportunity to propose some changes and improvements. After detecting that there was lacking of a structured overview of the products for which Datamedica was responsible for in the pharmacovigilance area, I had the opportunity to develop along with a colleague a database containing all products of interest, their MAH, and all the relevant information related to them. It was also necessary to develop a schedule for PSUR submission and for products' Marketing Authorization (MA) renewal. As so, a master database containing all products was created providing information on the scheduling for PSUR submission and renewals, according to the most recently released List of European Union Reference Dates and frequency of submission of Periodic Safety Update Reports (EURD) (available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/09/news_detail_001616.jsp&mid=WC0b01ac058004d5c1) lists publications in order to harmonize PSUR submission with European dates established for data lock point (DLP). During the process, it was of most importance to have in mind the Module VII - Periodic safety update report (22) of the GVPs and also the new pharmacovigilance legislation in what concerns PSUR submission exemption for generics.

Daily and Weekly Database Research

This database research is performed in order to find new safety information regarding a specific client's product, such as reported adverse drug reactions that resulted from product's administration, individual safety cases reported in the literature and safety studies performed with the product in question. This way, it is guaranteed that the client has access, every week, to updated safety information on its products and that individual case safety reports (ICSR) are notified to the authorities, if deemed necessary.

This search is performed using specific keywords for each product in several databases of relevance for the scientific community, such as PubMed. Afterwards, the new safety information resulting from the weekly database research is essential to complete the PSURs for the product in question.

Periodic Safety Update Reports

Preparation of PSURs was the activity that I had the opportunity to develop more in depth within the pharmacovigilance area. I had the chance to help preparing several PSURs and to assist in collecting the necessary information in order to complete all PSUR sections, as well as assisting in the PSUR submission process to the competent authority (INFARMED).

Due to the implementation of the new pharmacovigilance legislation, some aspects had to be altered whether in the PSUR format as in the scope of the information necessary to submit to the competent authorities. In order to do that, I had to read thoroughly in conjunction with a colleague the Module VII of the GVPs to guarantee that all new requirements were properly fulfilled. Furthermore, I had the opportunity to develop a new template for PSURs to be used within the company, which was in accordance with Module VII of the GVPs and the orientations provided there.

Renewals of the Marketing Authorization

The process of MA renewals also suffered some changes due to the new pharmacovigilance legislation. I had the opportunity to assist in the adaptation of the company's procedures to comply with the new requirements for MA renewal. In this specific case, I only assisted in the preparation of the documents directly related to the

pharmacovigilance functions that are an important part of the renewal process. As so, I was able to assist in the elaboration of the Summary of Pharmacovigilance System Master File and the Addendum to the Clinical Overview, which addresses the benefit/risk of the product, having into account the data from the previous PSUR and the cumulative safety and efficacy data available on the product (23).

Adverse Reaction Notification

As part of the pharmacovigilance functions, it is also important to serve as a point of contact for the authorities and healthcare professionals in what regards adverse reactions notification. Due to the new pharmacovigilance legislation, it is now mandatory that all occurrences are transmitted to the competent authority (INFARMED) through an electronic process, after the company being registered in EudraVigilance. During my internship I was able to understand how this process works and what are the necessary inputs to put it into practice, such as acquiring a MedDRA license.

I also had the opportunity to collaborate in a report of an adverse reaction occurred with a cosmetic product, which allowed me to understand the process of such notifications that involve a specific INFARMED's formulary and the contact with Centro de Informação Anti-Venenos (CIAV).

3.1.2. Quality Management

One of the tasks that I participated in was the reformulation and reorganization of the Quality System within the company. In this area, I was responsible, along with some colleagues, to review the company's Quality Manual and the Clinical Research SOPs.

3.1.3. Medical writing

Medical Writing involves a set of activities related to the communication process of clinical and scientific data. I have taken part in some activities such as elaborating a protocol synopsis, reviewing a study protocol and developing informed consent forms. These activities gave me an insight of the work needed to prepare the scientific rationale for a clinical study and correctly design scientifically valid study protocols.

3.1.4. Non-clinical Studies

Non-clinical studies are an essential stage in drug development, since they allow exploring safety and efficacy before administering the IMP to human beings. I have been given the chance to assist in the elaboration of a non-clinical development plan for a new oral vaccine. That required reading several European guidelines concerning adjuvants and animal studies, so that the developed plan was compliant with the European requisites for the development of vaccines and vaccines adjuvants. This was a very challenging activity that I never had the chance to perform before and which gave me the opportunity to expand my knowledge in the non-clinical development of a drug.

3.1.5. Other activities

The opportunity to collaborate in the (creative) efforts that are made in a small company to gain new projects was also given to me. My tasks concerned giving support to the proposals that were made to gain such projects, from preparing confidentiality agreements, to performing background research to create a rationale for the project and creating study flowcharts and presentations.

3.2. Specific Training – Clinical Monitoring

Clinical Trial Monitoring was the primary focus of my internship, hence when I arrived at the company the major concern was to give me an insight of the projects that were ongoing at the time and to define which tasks I would be performing in the scope of each project. My primary goals were to familiarize me with each of the project, by reading the trial protocols and other trial-related documents and to understand the status of each study (number of active sites, number of patients, site history, pending issues, etc).

Throughout my internship I was able to participate in two observational studies and eight clinical trials, performing mixed functions of clinical research associate and clinical trial assistant.

Figure 6 illustrates my participation in the different studies over time.

Figure 6 – Chronological distribution of the activities developed in each clinical study during the internship.

3.2.1 Observational studies

During my internship I had the opportunity to participate in two observational studies. Table 1 resumes the tasks that I have performed in each observational study.

Table 1 – Overview of the tasks performed in the scope of observational studies.

Study	***Therapeutic Area***	***Study Status***	***Tasks performed***
Odyssey	Renal Failure	Follow-up Visits	- Co-monitoring visits to collect patients' data and to perform SDV[1] - Introduction of collected data in the study database
SalfordLung Study	Asthma and COPD[2]	Initiation	- Selection of study sites - Study sites feasibility - Bibliographic research to support the development of the study in Portugal

[1] SDV – Source Document Verification
[2] COPD – Chronic Obstructive Pulmonary Disease

Bibliographic Research for Study Development

When working in a small size Full Service CRO it is vital to create study designs that fulfill the client's project objectives. In order to construct a successful project, background research needs to be performed. This research is generally a bibliographic research that helps constructing the rationale for the project and helps defining the better strategy that allows maximizing the information that can potentially be obtained.

Regarding this type of activity, I performed bibliographic research to help designing new projects, as well as research related to healthcare statistical data in order to calculate the adequate sample size.

Initiating a Study - Site Selection

Site selection is an important activity that allows identifying the investigators and sites that are thought capable of conducting the clinical trial in an appropriate way. This selection can be based on many factors, such as previous contact or experience with the center, existence of a reference center for a specific disease or condition, geographic reasons, the center being recommended by the coordinating investigator, among others.

In some cases, a pre-trial visit is conducted, in order to assess the feasibility of the site and the willingness of the investigators to participate in the trial.

When evaluating the sites, there are chronological steps that have to be performed.

Generally, the first step is to choose the sites, the second one is to choose the investigators and only then the sites are contacted.

From my personal experience, it is the function of the CRA/Clinical Research Manager (CRM):

- To identify and select potential investigational sites and investigators, having in mind the resources necessary for study conduction and the already known sites with whom contact has been established in the past;
- To establish contact with the potential investigators, through the most appropriate means of communication, whether by a telephone contact, by email or by a personal visit. This first contact is intended to briefly describe the study, study protocol, established timelines and to evaluate the interest of the investigator in conducting the study. A more detailed explanation on study procedures is provided after the establishment of a Confidentiality Agreement that the investigator has to sign;

- To evaluate the resources available at the site facilities and if they are suitable to conduct the study;
- To conduct Pre-Trial visits whenever deemed necessary;
- To negotiate the payment modalities.

As a CRA I performed several telephonic contacts in order to assess the potential interest of different sites in conducting a specific observational study. I also had to check the feasibility of the sites in order to make sure that those sites had the required resources to conduct the study.

Preparing Monitoring Visits

Preparing monitoring visits is one of the most important tasks in order to assure that all necessary procedures will be accomplished during the monitoring visit. During my internship I was responsible for identifying and preparing all procedures that had to be done during the monitoring visits. Regarding the Odyssey study (see table 1), preparation of visits was of extreme importance because the electronic Case Report Form (eCRF) was unavailable and as such the patient number had to be checked and follow-up forms in paper format had to be provided for data collection.

When preparing monitoring visits several aspects have to be taken into account:

- Site Status;
- Patient status and number of active patients;
- List of pending issues for the site;
- Necessary documentation that needs to be signed by the investigator or other; clinical trial staff;
- Documentation that has to be archived on site;
- Establishing an acceptable visit duration in order to solve all necessary issues;
- Other aspects that have a direct impact on visit conduction.

Monitoring Visits - Co-monitoring visits to collect patients' data and to perform SDV

Monitoring visits are a mean through which it is possible to verify and control several aspects related to clinical studies. In observational studies, monitoring visits also play an important role since they allow to verify the reliability of the data obtained. Normally,

monitoring visits in this context are less labor intensive compared with clinical trials, but require adequate preparation and conduction. The monitor has the responsibility to verify if the study is being conducted in accordance to the established protocol and applicable guidelines and regulations.

Visits to the center are generally conducted on a face-to-face basis but, depending on the complexity of the study, a phone contact can also be made in order to obtain updated information on the study progress.

Generally, the essential documents to be reviewed during a monitoring visit are the ICF, the CRF, the patient's medical file in order to perform SDV, and the Investigator's File (IF).

The ICF is a vital document that needs to be verified in order to assure that the patient has given his/her consent to participate in the study before any study procedures are initiated. The consent needs to be correctly signed and dated by both patient and investigator. When the subject is not able to sign, the subject's legally acceptable representative can sign on his/her behalf. The monitor has the obligation to check if the ICF was correctly obtained, is adequately signed and dated and adequately kept.

The IF needs to be up-to-date and the monitor has to check the file to guarantee that all necessary documents are correctly archived and for those that require signature, correctly signed.

The information collected in the CRF needs to be verified through patient's medical records. In most of the studies it is necessary to perform this checking, called SDV. Sometimes, it is established per protocol that only a percentage of the study population will be checked, e.g. 10% (so called partial SDV). In case of several findings, SDV may be performed for the whole study population. In this way, it is guaranteed that all information present in the CRF is according to the patient's medical records.

During my internship I performed co-monitoring visits to verify follow-up information. Due to the fact that there were some technical problems with the eCRF in the scope of the Odyssey Study (see Table 1), it was not possible to use this tool to verify information. As so, it was necessary to resort to other solutions, such as a paper CRF for recording data. When I was fully integrated in the study, I develop a more user-friendly paper CRF that could be sent to investigators and filled electronically by them. Due to this problem, some

follow-ups had to be obtained through phone contact, so that the investigator was able to provide all necessary information to complete the follow-up.
In total, I performed approximately 7 co-monitoring visits and 5 monitoring visits alone in the scope of this observational study; and 4 phone contacts to obtain follow-up information.

Database Filling - Introduction of data in the study database

Generally, the data collected through an eCRF is extracted to a format in which it is possible to perform statistical analysis. However, due to the technical problem that has occurred with the eCRF in the Odyssey Study, it was not possible to update the patients' records electronically. Hence, it was necessary to introduce this information manually, using a datasheet document, so that afterwards the data could be analyzed. This task had to be performed whenever new data arrived or were collected, so that the temporary database could be updated.
This task occupied plenty of my time during my internship, since it was rigorous and time-consuming. I also was responsible of preparing training on how to insert data in the datasheet document created for the study so that all my colleagues could help insert the necessary information.

3.2.2 Clinical Trials

In the scope of clinical trial monitoring I had the opportunity to participate in eight clinical trials. The overview of the tasks that I performed in each clinical trial can be seen in Table 2.

Table 2 – Overview of the tasks performed in the scope of clinical trials.

Study	*Study Type*	*Therapeutic Area*	*Study Status*	*Tasks performed*
Keplat-PT01	Phase II	Rheumatoid Arthritis	Initiation and Submission Phase	- Preparation of necessary documents to perform the study submission - Submission to the Competent Authorities
ANG11-01	Phase IV	Chronic Back Pain	Submission Phase	- Submission to the competent authorities (additional information request) - Site selection and site feasibility
HPV-015	Phase III	Gynecology	Monitoring Phase	- Co-monitoring visits (SDV, accountability) - Elaboration of monitoring visit reports - Submission of substantial amendments, IB and study insurance
HPV-062	Phase IIIb	Gynecology	Monitoring Phase	- Co-monitoring visits (SDV) - Elaboration of monitoring visit reports
HPV-066	Phase IIIb	Gynecology	Monitoring and Roll-Over Phase	- Co-monitoring visits (SDV, accountability) - Elaboration of monitoring visit reports - Notification of protocol deviations to the competent authorities
L00070 IN 303 B0 VICTORIA Study	Phase III	Oncology (Breast Cancer)	Monitoring Phase	- Co-monitoring visits (SDV) - Collection of follow-up forms - Collection of pending imaging exams for the TMF - Collection of pending documents for all sites
L00070 IN 308 BO	Phase III	Oncology (Breast Cancer)	Monitoring and Termination Phase	- Resolution of queries through data clarification forms - Collection of pending documents for all sites
PM0259 CA 227 J1 NAVOTRIAL	Phase II	Oncology (Lung cancer)	Termination Phase	- Notification of study termination to the competent authorities

Selecting and Planning – Site selection and site feasibility

Site selection is a key task as already stated under the section 3.2.1. Site selection for clinical trials can be more complex and rigorous comparatively to site selection for observational studies. Clinical trials follow a more detailed protocol often involving laboratory measurements and administration of the IMP, which requires the availability and interaction of different hospital services, such as nursing, pharmaceutical services and laboratory services. As so, the criteria used for selecting the sites should be restrictive and properly pre-defined.

The selection of investigational sites and investigators has several objectives:

- To select qualified investigators with training and experience in order to assure the proper conduction of the clinical trial;
- To know the organization of the department and the number of staff members;
- To check if the investigated pathology is available;
- To obtain the number of patients with the pathology in observation per month/per year and how they are treated;
- To understand where are patients attended: in-patient/out-patient;
- To verify the equipment available at the site.

The sponsor is also responsible for selecting a coordinating committee or a coordinating investigator in the case of multicenter trials, to facilitate the trial logistics and conduction.

A Pre-Study Visit to the potential study center can also be conducted to verify the adequacy of the clinical facilities and the qualifications of the site staff. This visit can also be useful to provide the investigator with all necessary information about the trial, through a brief explanation of the trial protocol and other relevant documents. The investigator and the institution should have enough time to review the trial protocol and the Investigator's Brochure, as well as all the information provided by the sponsor, before signing any type of agreement with the sponsor.

At this phase, it is necessary to obtain from the investigator and from the site:

- A confidentiality agreement for the disclosure of study information;
- A signed agreement to conduct the trial in compliance with GCP, the protocol, the sponsor SOPs and all applicable regulatory requirements;
- A signed agreement permitting monitoring, auditing and inspection;

- A signed agreement stating that the investigator/site is willing to maintain the study-related documents for the period of time indicated by the sponsor

To confirm these arrangements, the sponsor and the investigator/trial site should sign the protocol, or any other specific document created for this purpose (6).

I was able to participate in the activities of site feasibility and selection for two clinical trials: ANG-1101 and Keplat-PT01 (see Table 2).

Preparing Study Essential Documents for Submission

Initial Study Submission is a process that needs to be planned very carefully. All essential documents such as study protocol, study synopsis, ICF, patient diaries and CRF should be reviewed.

When those documents are sent by an international sponsor, it is necessary to translate them to the Portuguese language, namely study synopsis, ICF, patient diaries and patient questionnaires/handouts.

At the beginning of my internship one of my initial tasks was to translate the ICF, protocol synopsis and patient diaries of the Keplat-PT01 trial (see Table 2), in order to perform the study submission to the competent authorities. These translated documents were afterwards approved by the Portuguese sponsor's representative.

The protocol needs to be signed by all Principal Investigators (PI) and by the sponsor and this can be a difficult task, but one that is crucial for the study submission. I assisted in the preparation of the protocol signature sheets and the request for signatures to the PIs.

Another aspect that is important to prepare a draft of the financial agreements to be established with study sites and with external vendors in case they exist. These agreements need to take into account the available budget defined by the sponsor, the overheads charged by each hospital, the distribution of the payments (percentage form distribution) that is generally established by the hospital's internal administrative procedures and all the study-related procedures, such as number of visits, complexity of visits and laboratory procedures. In some cases, site staff has to be compensated for the services provided and an emolument should be taken into consideration when preparing the budget for the center.

Once the budget for each center is prepared, the elaboration of the financial agreements (first draft) can take place. Some study sites have their own template for financial

agreements and when this happens the template provided by the site should be used. To know if the site has a model that can be used, it is necessary to establish contact with the site and to try to obtain all the necessary information on the submission process. This information can be obtained at the time of the selection of feasible sites for study conduction.

I had the opportunity to participate in the preparation of budgets and financial agreements in the scope of ANG-1101 and Keplat-PT01 trials (see Table 2). I also collaborated in the process of drafting financial agreements with external vendors, i.e. pharmacies and laboratory for analysis, which was necessary due to the fact that the selected site was not capable of providing these services in the scope of the clinical trial. Both financial agreements with sites and external vendors are part of the study submission to the competent authorities. Agreements with external vendors must comply with the orientations provided by CEIC on: "Participation of external entities to the Clinical Trial sites for performing complementary diagnostic exams" ("Participação de entidades externas aos Centros de Ensaio para a realização de exames complementares de diagnóstico").

To prepare the agreements with the external vendors it was necessary to request a cost estimate for the services required. The cost estimate provided by the external vendor to a specific site should be taken into account when elaborating the final budget and distribution of funds for that specific site.

There are other study-related documents that need to be prepared in case they are not provided by the sponsor. In the scope of Keplat-PT01 trial (see Table 2), it was necessary to create study logs such as Investigational Product Prescription and Dispensing Log and Patients Handouts, such as Daily Register of Medicinal Product Use. It was also required to prepare a Clinical Trial Labeling for the IMP. It was necessary to assure that the labeling developed was in accordance with all applicable regulations, namely Article 32 of Portuguese Law 46/2004, of August 19th, Article 14 of the Directive 2001/20/EC, Article 15 of the Directive 2003/94/EC and Good Manufacturing Practices (GMPs).

Study Submission to the Competent Authorities

According to Portuguese Law 46/2004, of August 19th, in order to conduct clinical trials it is necessary to obtain authorization and favourable opinion from INFARMED and CEIC, respectively.

As a trainee, I had the opportunity to carry out this type of submissions. Before performing them, it was crucial for me to read the instructions for submissions present in the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial- CT-1". Herein are stated all requirements that need to be fulfilled for the different types of submissions to the competent authorities, namely Clinical Trial Application, Substantial and Non-Substantial Amendments and End of Trial Declaration.

Obtaining the EudraCT number

Before submitting the request for clinical trial authorization, the sponsor must obtain a unique EudraCT number for the clinical trial. This number is obtained by registering the clinical trial in the European clinical trials' database and allows identifying in a unique manner the clinical trial, whether it assumes a multicentric design or not. The applicant must provide some basic elements and afterwards receives a confirmation email with the assigned EudraCT number. After obtaining the EudraCT number, the applicant can register the clinical trial and obtain the so called XML file that is necessary to submit the study to the competent authorities. This XML file is the "Annex 1 -Application Form: Request For Authorisation Of A Clinical Trial On A Medicinal Product For Human Use To The Competent Authorities And For Opinion Of The Ethics Committees In The Community".

Submission to INFARMED and CEIC

After obtaining the EudraCT number, the sponsor is ready to make the application to the Portuguese competent authorities: INFARMED and CEIC. This submission can be done in parallel.

It is necessary to understand that these submissions undergo sequential phases:

- the **validation phase**, in which the competent authority validates the request, considering that all necessary requirements for submission are fulfilled;
- the **additional information request**, in which the competent authority raises questions concerning the clinical trial;
- the **deliberation phase**, in which the competent authority decides in favour or not of the authorization to perform the clinical trial.

The Submission to CEIC should be performed according to the instructions provided by this entity in the documents "Instructions to the applicants for the submission of an opinion request to CEIC" and "Instructions to the Applicants – CD-ROM organization".

The Request for Authorization for Clinical Trial Conduction to INFARMED must comply with the requirements established in the orientations provided by this authority "Instructions to the Applicants of a Clinical Trial Application" and "Instructions for the information electronic submission".

The submission to both authorities is in mixed format, paper and electronic. In a general way, the documents to be submitted to INFARMED and CEIC are:

In paper format:

- Cover letter directed to the President of CEIC or INFARMED;
- Proof of fee payment to INFARMED, according to Portaria 396/2005, of 7th of April (24);
- Annex I (Clinical Trial Application Form) correctly filled in and signed by the applicant;

In electronic format (CD-ROM with all required documents organized in folders according to the verification list provided by each authority):

- Proof of fee payment to INFARMED, according to Portaria 396/2005, of 7th of April;
- Annex I (Clinical Trial Application Form) correctly filled in and signed by the applicant;
- XML File, from EudraCT database;
- Protocol and respective amendments;
- Investigator's Brochure;

- Information about the IMP:
    - Investigational Medicinal Product Dossier (IMPD);
    - Summary of Product Characteristics (SmPC) (if available);
- Other requested elements from the Verification List for the clinical trial submission.

During my internship I had the opportunity to be involved in the initial submission of two clinical trials, as well as in the answer to the additional information request made by the competent authorities. I prepared the documents for submission, the folder organization and the cover letter necessary for each competent authority.

Submission to CNPD

In Portugal and according to Law nr 67/98, of October 26th (25), the Law of Personal Data Protection, it is necessary to request Authorization to CNPD in order to perform activities that involve the handling of personal data. The notification to CNPD is performed through a specific online form, the "General Notification Form" (Formulário Geral de Notificação) available at the institution's site.
The applicant must fulfill the form and submit it online. This form requires mainly the following information:

- Who is responsible for the data handling
- What is the objective of the data handling
- What is the personal data that is going to be obtained
- How is the collection of data going to be performed
- If there is any communication of the collected data to third parties
- Who will have access to the collected data and what are the security measures applied to keep the confidentiality of the records

To validate the notification it is necessary to pay a fee within three days after the submission of the electronic form.

I had the opportunity to perform a submission to CNPD in the scope of the initial submission for Keplat-PT01 study (see Table 2). During this submission I learned that it is important to provide this Commission with some essential documents, such as CRF, which contains the description of the data being collected, to help accelerating the decision process. I also realized that it is important to act pro-actively and foresee the questions going to be raised, such as collection of the variable ethnicity, which is something that can be considered discriminatory and needs to be scientifically justified.

Study Submission to Institutional Review Board and Institutional Ethics Commitee

Study Submission to the Hospital's Ethics Committee is required in order to obtain the Site's approval for the clinical trial implementation. The submission requirements vary according to the Site and as so it is necessary to gather information on the requirements for each site and then start preparing the submission. At most sites, the submission cannot be performed until the trial has obtained authorization from INFARMED and favourable opinion from CEIC.

Generally, the requested documents for a complete evaluation are:

- Protocol synopsis;
- Protocol;
- Protocol Signature Page;
- ICF;
- Investigator's Brochure (IB);
- Approval from CNPD and INFARMED and opinion from CEIC;
- Curriculum Vitae of the Principal Investigator;
- Study Insurance Policy;
- CRF;
- Financial Agreement to be established with the site;
- Authorization from the Clinical Director to perform the clinical trial;
- Declaration of the conformity of the site facilities and resources (including constitution of study team).

I have participated in the preparation of the study submission to the study sites by obtaining the site submission requirements, organizing the dossiers for submission and

elaborating a cover letter directed to the President of the Hospital's Board and Ethics Committee.

Other Types of Submissions

During a clinical trial, there are other types of submissions to the competent authorities that need to be performed, such as Substantial Amendments and End of Study Notification/Declaration.

According to the CT-1 (26), an amendment is considered substantial when the alteration has significant incidence on the safety and physical or mental integrity of the study participants or on the scientific value of the clinical trial.

This type of alteration can be notified only to CEIC or to INFARMED or both, depending on the information that has been modified.

For this type of submission it is required to fulfill a specific form, the Annex 2 - Substantial Amendment Notification Form. The submission is performed in a mix format, paper and electronic. The content of the Notification is, in a general way, the following:

In paper format:

- Cover Letter explaining the rationale for the amendment, signed and dated by the applicant;
- Annex 2 - Substantial Amendment Notification Form filled in, dated and signed by the applicant;
- Proof of fee payment to INFARMED, signed and dated.

Electronic format:

- Cover Letter explaining the rationale for the amendment;
- Annex 2 - Substantial Amendment Notification Form filled in, dated and signed by the applicant;
- New and superseded version (in track changes) of the modified document or the whole new document (according to the folder scheme defined by the authorities);
- Other relevant documents that may provide a deeper understanding of the rational for the amendment.

It is important to mention that if the alteration introduces changes in the information provided to the Clinical Trial Application, a copy of the modified XML file and a version with the changes highlighted should be provided.
I had the opportunity to perform substantial amendments in the scope of clinical trials during my internship. I had the responsibility of preparing the files for submission, including filling in Annex 2, as well as writing the cover letters.

When a clinical trial terminates, it is necessary to notify the competent authorities of its finalization within 90 days (in normal conditions). The definition of the clinical trial end should be defined per protocol.
To notify the authorities it is necessary to fill in Annex 3 - Declaration of the End of Trial Form. The submission is also made in a mix format, paper and electronic. The content of the Notification is, in a general way, the following:
In paper format:

- Cover Letter signed and dated by the applicant;
- Annex 3 Declaration of the End of Trial Form signed and dated by the applicant.

In electronic format:

- Cover Letter signed and dated by the applicant;
- Annex 3 Declaration of the End of Trial Form signed and dated by the applicant;
- End of Trial Conclusion Letter stating that the trial has terminated in all Member-States/third countries, signed and dated by the applicant.

I had the opportunity of submitting to the competent authorities the end of trial declaration for the NAVOtrial (see Table 2). I was responsible for filling in Annex 3 and preparing the submission.

Documentation Archive

Archiving study documentation is a fundamental task in order to keep all files up-to-date with all trial-related information. The list of essential documents to be archived needs to be

in compliance with ICH-GCP. The study documentation can be at any time inspected by local and international authorities.

There are several types of dossier to archive study documentation and these can assume several designations:

- The Study Country File, intended to archive all the study general study documentation and that is kept within the sponsor facilities;
- The Center File, specific for each study center and archived in the sponsor facilities;
- The Investigator File (IF), to be archived in each center.

In addition to having a physical archive, the digital versions of each document should also be kept in an electronic server, with restrict access. In that way both security and accessibility of the documents to authorized personnel can be assured. All the dossiers need to be updated as the study progresses.

When working for an international company, translations of the correspondence exchanged with the competent authorities are necessary. These translations need to be archived in both virtual and physical files alongside with the original documents.

During my internship, one of my functions as CTA was to archive properly all the study documentation and to keep the study files up-to-date. It was also necessary to find missing documentation and solve some pending issues by request of the international study team. This required a constant contact with the study site and study staff to try to obtain the missing documentation. I was also responsible for translating all the necessary documentation, archiving it and sending it to the international study team.

I also had the opportunity to prepare and organize in first-hand the TMF and Centre File for the studies that were in submission phase at that moment. This activity obliged me to follow Datamedica's SOPs, but at the same time to have critical thinking and reassess the documentation required by the SOPs.

One of the things that I helped to implement at Datamedica was the implementation of a document tracker that allowed to quickly understand how many versions of a document existed and which one was the current version. It also allowed visualizing if the versions

had already been submitted to the competent authorities, the date of the submission, as well as the approval date.

Preparing Monitoring Visits

Though the process of clinical trials is more complex, the principles applied are the same as the ones described for observational studies in section 3.2.1.
It is fundamental to know the follow-up status of each study participant and to define which part(s) of the CRF is (are) going to be monitored. The monitor also needs to know if it is supposed to perform partial or full SDV, according to sponsor's monitoring guidelines. In the study status, the monitor should check if there are any queries pending for the site, in order to solve them with the investigator during the monitoring visit.
I assisted in preparing several monitoring visits, taking into account all the pending issues for the site (including queries), the site status and all activities that should be performed during the visit. I also prepared several "note-to-file" for the investigators to sign regarding items such as informed consent forms, missing documentation, IMP disposal and other issues. "Note-to-file" documents are intended to clearly explain any detected discrepancies and specify the reason for the error or omission that they refer to and should be filed with the document to which they apply.

Monitoring Visits

Monitoring of a clinical trial by the sponsor is a critical task and a requirement established by GCPs. Monitors establish a communication bridge between the sponsor and the study site and they can provide valuable insight on the site performance as they are a point of contact for all the study staff.
The timing for the monitoring visits is established by the sponsor but depends on the study design, the complexity and length of the study and also the performance of the study site.
The essential task of the monitor is to guarantee that the study is conducted according to the protocol, ICH-GCP, sponsor's SOPs and all applicable regulatory requirements.

During a monitoring visit there are several items that a monitor may cover:

- Protocol Adherence
- Subject recruitment and informed consent form
- Occurrence of safety events
- Issues regarding site administration, such as regulatory approvals and site staff training
- Storage, handling and return of IMP and Drug Accountability
- Record keeping: registry of data in the CRF and in the patient's clinical file.

It is very important to check protocol adherence in order to understand if the Principal Investigator's (PI) management of the study activities are adequate. A discussion of the study progression with the PI is mandatory to verify if the PI has any doubts and if any protocol deviations have occurred.

The monitor also needs to verify if the ICF forms have been properly obtained, signed and filed and if there are any consent withdrawals. It is also vital to check the site recruitment rates and to encourage the PI to recruit.

The occurrence of safety events also needs to be verified, such as SAEs, pregnancies and medical incidents in order to verify if the recommended procedures in those circumstances were followed. The acknowledgment of receipt of new safety information released to the PI, such as Investigational New Drug Safety Reports (INDSRs), Periodic Safety Reports to Investigators (PSRIs), Investigator's Brochure (IB), Dear Investigator Letter, should be obtained.

Items regarding site administration include new issued protocol amendments and new study related materials, for example. The monitor also needs to verify if the regulatory documents and study correspondence is adequately maintained and filed; if the site equipment and facility certification and licenses are maintained; if there are any changes in site staff or facilities and if the PI and site staff are adequately trained on the current protocol amendment and study procedures.

Some aspects regarding the IMP also need to be taken into account, for example:

- performing accountability of the product;
- verifying if the IMP is sufficient and is within expiry date;
- verifying storage and maintenance according to protocol requirements;
- verifying if IMP shipment records are present, signed and filed appropriately;

- confirming if dispensing records are accurate and up-to-date and if IMP was destroyed or returned.

One of the most important aspects to be monitored is record keeping. The monitor must verify if:

- Source documentation is available, adequately maintained and archived;
- CRFs and other data collection tools are completed in a timely and accurate manner;
- Data queries are resolved in a timely manner and filed properly;
- The SDV plan is adequate for the site in question.

During my training, I have performed co-monitoring visits in the scope of clinical trials. In these visits I helped performing the following tasks:

- To confirm if informed consent and respective amendments, if any, were properly obtained, signed and dated, obtained before any study procedure and if the patient has been given a copy;
- To verify the storage conditions of the investigational product, assuring that the IMP was kept at recommended temperature through the temperature log registries;
- To verify the drug dispensing and administration to assure that the IMP was only administered to eligible subjects, at the right doses and according to protocol. This verification has been made through the dispensing and administration logs present at the pharmacy;
- To confirm the reception and return of IMP and the respective acknowledgment of receipt in appropriate forms, cross-checking with the information on the quantity of supplies received, prescribed and returned;
- To perform Drug reconciliation, which is an accountability process. This process considers the amount of drug supplied to the site, the administered doses to patients and the medication sent for destruction or returned to sponsor, allowing to track the drug supply chain;
- To communicate in the appropriate electronic tool the occurrence of temperature deviations in the transport and receipt of the IMP at the site;

- To perform Source Data Verification (SDV), verifying if the information contained in the source documents correspond to the information registered in the CRF and if these records are complete, accurate and adequately filed;
- To request the PI to justify, complete or correct any missing or incorrect data;
- To collect follow-up CRFs in paper format in accordance with protocol requirements;
- To verify the IF for essential documents required to be filed by GCPs and sponsor SOPs;
- To resolve inconsistencies and queries in conjunction with the PI between paper CRF and eCRF, through the filling of Data Clarification Forms (DCFs) provided by the study data management team.

Monitoring Visits Follow-up Activities

After every monitoring visit there are always actions that need to be taken. First of all, if there are any urgent follow-up actions to perform these should be given priority.
If there are pending issues with the site, a follow-up contact should be made in other to understand if the problem has been solved.
Every contact, including monitoring visits, generates a monitoring visit report or a contact report. This report should be filled in within 5 working days, according to ICH-GCP (6).
Different sponsor have different report templates, but in a general way they cover similar aspects such as:

- Discussion of study progress with PI
- Verification of ICF
- Verification of recruitment rates
- Occurrence of SAEs/pregnancies/medical incidents
- Occurrence of protocol deviations
- Aspects regarding site administration (training and staffing)
- Storage, handling and return of IMP
- Laboratory Management
- Data Collection Management and SDV Strategy.

I received training in order to learn how to fill in monitoring visit reports and afterwards I was responsible for elaborating monitoring visit reports of the visits that I co-monitored. In studies where there was the need to collect paper CRFs during each visit and afterwards to send them to the sponsor, I helped preparing the sending of the collected documents to the international study team, filling in CRF transmittal forms and transport documentation, e.g. airway bills.

Close-out Visits

Site close-out visits mark the end of a study at a specific site. Site close-out visits are generally performed to the hospital service and to the pharmacy. These visits can only be done when all files, both institution and sponsor, are reviewed by the monitor and when there are no pending issues for the site. The monitor needs to confirm that all required documents are filed in the correct archive (6).
When working for pharmaceutical companies as a CRO, normally the sponsor is the one who decides when to perform a site close-out visit. This normally happens when:

- The last patient has performed the last visit (last patient, last visit – LPLV) according to protocol;
- No further subjects are to be enrolled and no further data is to be collected;
- When all CRFs are correctly completed and all queries are solved;
- When the study is cancelled prior to recruitment or is stopped prematurely or even when the study does no longer have the approval from the competent authorities.

The competent authorities must be notified of the end of the study through Annex III – Declaration of the End of the Trial, as described in section 3.2.2 Clinical Trials – Other types of Submissions.

During the Close-Out Visit the monitor should ensure the following:

- That all CRFs have been corrected, collected and archived adequately;
- That all SAEs and other events such as pregnancy events have been reported to the monitor, sponsor, competent authorities and other parties, as defined per protocol;

- That all SAEs are recorded and followed-up until its complete resolution in accordance to what is defined per protocol.

A final trial close-out monitoring report should be made in order to guarantee that all activities required for the study close-out were performed and that all documents are archived in the appropriate files (6). These files should be kept available for consultation up to 2 years after the end of the trial, according to ICH-GCP.

As a trainee, I participated in some activities regarding site-close-out, namely the resolution of queries through DCFs with the investigator. As for the close-out visit itself, I participated as an observer in those activities. I collaborated in the filling of the necessary forms and the gathering of missing documentation.

4 Discussion

The activities performed during my internship were very useful for my professional and personal growth and enrichment. The contact with the daily working reality provided me an insight of all the problematic aspects related to this type of activity.

Acquired competencies and academic formation importance

This internship has given me the opportunity to develop my skills and competences as a clinical research professional and has allowed me to put into practice the knowledge acquired during my academic formation.

I had the possibility to understand how different departments work together to achieve a goal and how each and every person can make the difference. Working as a team in a structured and organized manner is half way to success. Transparent communication and team building are core values that a multidisciplinary team should have. These allow the subjects to grow as a team and to easily overcome obstacles.

I also learnt that opportunities for business must be created and others seized, so that the sustainability of the company can be maintained. When creating new business opportunities, team work assumes a key role since subjects desire to reach the same goal and are motivated to do it.

Since the company suffered some structural changes during my internship, I had to assume an autonomous role sooner than expected and to work together with my colleagues to find answer for some difficulties that arose. These gave me an enormous capacity of dealing with problems and promptly solve them, always trying to find the best solution, which was something that my academic formation also trained me for (problem solving).

In this opportunity I could develop technical skills in Clinical Trial Assistance and Clinical Trial Monitoring, since my tasks involved activities in Study Start-Up and Monitoring. This has given me a practical notion of the initial contact with the sponsor, gathering all necessary documentation for study submission, initial site contact, site feasibility and study submission to the Competent Authorities and to the selected sites. Furthermore, I have developed activities specifically concerning study monitoring: follow-up visits to assure protocol and ICH-GCP compliance, telephone contacts, investigational drug

accountability, elaboration of monitoring visit reports and center and pharmacy close-out visits.

I also had the opportunity to perform several types of submissions to the competent authorities which included: clinical trial application, substantial amendment notification, end of study notification, protocol deviation notification and study insurance update notification.

The fact that I had to perform all these activities gave me a vast knowledge of all the requirements that are needed to conduct a clinical trial and truly allowed me to become a clinical research professional with a rich and complete experience in clinical trials.

One advantage was the fact that I also had to carry out several tasks in the pharmacovigilance area, such as PSUR elaboration and weekly database research, which allowed me to understand that pharmacovigilance assumes a transversal role that gives support when needed to the clinical trials area.

With this experience, I was able to develop my social and personal skills such as autonomy, organization, efficiency, time management and interpersonal communication. The obligation to comply with specific timelines in several studies running at the same time and the contact with several investigators and even with competent authorities contributed for this development. I also gained sense of responsibility, proactivity and evolved my verbal and non-verbal communication skills.

I have learned that accurate planning of activities is essential, since planning allows categorizing the actions that need to be done. In this way, it is possible to identify what is a priority and what is not. Planning saves time and resources, since the energy can be focused on the tasks needed to be performed urgently. I also understood that good planning should be accompanied by flexibility and adaptability, because in clinical research circumstances can change rapidly and when that happens it is necessary to reorganize what was initially planned.

My academic formation was extremely useful in order to perform the tasks that were assigned to me at Datamedica, Lda. Both the Bachelor Degree in Biomedical Sciences as well as the Master Course in Pharmaceutical Medicine have given me specific theoretical

foundation that allowed me to become rapidly autonomous and to assume a key role in every activity developed.

The excellent academic formation has allowed me to obtain an excellent knowledge of all applicable legislation and regulations in the scope of clinical research which helped me in tasks such as:

- Study submission to the competent authorities – knowledge of the authorities' role in this process and knowledge of the requirements for study submission were very important;
- Study monitoring – good knowledge of ICH-GCP and the role of the monitor became essential;
- Pharmacovigilance – awareness of the new legislation (July 2012) and the changes introduced by it, as well as other pharmacovigilance aspects and definitions.

The extracurricular activities in which I was given the opportunity to participate in the scope of the Master Course also provided me on-the-field insight concerning the implementation of observational studies, from ICF and study logs design to study submission to the Institutional Review Board (IRB) and Institutional Ethics Committee (IEC) of the study site.

Milestones in Clinical Trial Monitoring and difficulties encountered during the internship

Site Feasibility

Site Feasibility is an activity of extreme importance, because it is crucial to assure that the site complies with all the requirements for study conduction. This activity requires that the monitor or CRA has an overview of the project and its objectives and possesses an in depth knowledge of the study protocol. In this way, it is easier to make a list of potential sites and verify if they are capable to give response to the necessary requirements written down in the protocol. This involves establishing contact with several institutions, where the monitor has to explain in a simple and concise manner what is required to implement the study at the site.

Study submission to the Competent Authorities

Study submission to the Competent Authorities is a major step that has to be carefully planned. All the necessary documents need to be gathered and all signatures from all the parties need to be collected. This is a process that can take some time to prepare. The study should only be submitted to the Authorities when all the necessary documentation is properly collected and all study details are defined (except for financial agreements with the centers which are not submitted in their final version).

Once the study has been submitted, the sponsor has to be prepared to give prompt response to any additional information request from the Competent Authorities (i.e. INFARMED and CEIC).

Study Submission to Study Sites

Study Submission to study sites is generally a process that only starts once the approval of the competent authorities is obtained. To obtain authorization from the study sites is a very bureaucratic process that can last from 2 to 6 months. The time for study approval by the IRB and IEC is too long and is a factor that delays the study start-up and is posing a problem for the involvement of Portugal in international studies. Besides that, some selected sites may not be very familiar with the reality of clinical studies and therefore do not know how to properly conduct the process.

Sites have different requirements for submitting studies, which forces to prepare a personalized submission for each site. Also, these requirements may change over time and a constant update is necessary, contributing for even more delays in the process.

However, some sites are very well organized and prepared to receive clinical studies, where others are still not aware of this reality and it seems that it is due to a lack of information related to this subject.

Study Monitoring

Study Monitoring can be a difficult process when the investigator is not able to be contacted or not available to schedule a visit to the center. For example, there are investigators that stop performing the tasks delegated to them when they have no more study payments to receive. Others, since they do not receive incentives for conducting the study, delegate their tasks to their secretaries, which have no competencies to perform such

tasks. This often happens in observational studies, where it is more likely not to exist financial compensation.

The process of SDVcan also be a time-consuming process, in particular when paper CRFs are used and when the patient's clinical file is not in electronic format. The amount of information registered in the patient's file can also create difficulties in the monitoring process since many times not all the required information is written-down.

Another aspect that complicates the monitoring process is the fact that a new monitor can become part of the study already in follow-up phase or near the end phase without a proper handover of the monitoring functions and responsibilities has been done. In this cases, it can be very complicated to understand all that has been done over time, especially when the studies in question are studies that are ongoing for many years. Usually, these studies have pending documents and issues that were not previously solved and that the new monitor needs to solve promptly.

Site and pharmacy close-out

The close-out process of a clinical trial is never an easy process, especially when it is a study of a long duration and many people have been part of the study staff. Closing a site implies solving all pending issues and gathering all the missing documentation. This becomes difficult when the site staff is no longer working at the study site. As so, ending a study in a specific site has to be prepared carefully and involves some additional effort from the monitor in order to solve all issues.

In a general way, I believe that Portugal has several disadvantages in the area of clinical research that can be overcome to make the country an attractive place to conduct clinical trials. Here, I give some suggestions that I believe would make the difference and that result from my experience during this internship:

- To create specific legislation for observational studies and create harmonized requirements to submit this type of studies to the institutions (hospitals, clinics, etc);
- To create harmonized orientations for the submission of clinical trials to the institutions;

- To create awareness at population level about clinical research and perhaps authorize advertising of clinical trials under supervision of CEIC;
- To create sessions with both pharmaceutical industry and hospital's boards in order to emphasize the importance of clinical trial implementation and conduction;
- To create methods for networking and for sharing information between all healthcare professionals and people involved in research and development;
- To optimize the assessment/approval timelines for INFARMED, CEIC, CNPD and hospital's administrations, in order to try to match the approval times in other European countries;
- To develop a structure that would be capable of coordinating all national clinical investigation;
- It should be enforced a national program to support clinical investigation;
- To create pilot-centers for the conduction of clinical trials in Hospital Units that are prepared for such.

5 Conclusion

My 9-month internship experience was very challenging in many aspects and has allowed me to grow as a clinical research professional. I have realized that working in a Full Service CRO gives a different and broad perspective of all tasks that can be performed to further improve clinical research and the relationship with pharmaceutical companies. This experience has allowed me to improve my skills at every level, feeling truly capable of performing tasks in multiple areas.

I believe that my academic formation gave me a great advantage, so that I could already perform more practical tasks without the need for intensive training. The Master Course in Pharmaceutical Medicine is directed to the investigation, development, evaluation and approval of health products and properly prepares the student to become an active part of this process.

This experience also allowed me to understand the active role of a monitor in clinical trials and how it is important to embrace new initiatives that can foster innovation and to propose new and challenging ideas. I also understood that clinical trials represent a mean through which many patients have access to innovative medicines that can change their lives and as so I believe that every effort must be made to make Portugal an attractive place for clinical trial implementation.

After this 9-month experience, I felt that I have gained knowledge and experience to enter the reality of the working world and I also felt that I have grown personally and professionally, evolving as a person and realizing that in the future I certainly would like to work in this area.

As final conclusion, I believe that my internship objectives were met and for the future I would like to continuously improve my skills and knowledge in order to build a fruitful and successful professional career within this function.

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