Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2014

ANA RITA DOS SANTOS NOBRE

RELATÓRIO DE ESTÁGIO SOBRE MONITORIZAÇÃO DE ENSAIOS CLÍNICOS NUMA CRO FULL SERVICE

CURRICULAR TRAINING REPORT ABOUT CLINICAL TRIALS MONITORING ON A CRO FULL SERVICE

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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 orientação científica do Professor Auxiliar José Carlos Fontes das Neves Lopes do departamento de Física da Universidade de Aveiro e da Doutora Teresa Margarida Torcato da Conceição Proença de Almeida, Diretora de Operações Clínicas da Datamédica, Serviços e Consultoria em Bioestatística, Lda.

Curricular training report to be presented to the University of Aveiro to fulfill the necessary requirements for the Master's Degree in Pharmaceutical Biomedicine, held under the scientific guidance of José Carlos Lopes, Assistant Professor, Department of Physics, University of Aveiro and Teresa Almeida, Clinical Research Manager at Datamédica, Serviços e Consultoria em Bioestatística, Lda.

Dedico este trabalho aos meus pais, pela força, fé e coragem.

o júri

presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático, Universidade de Aveiro
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agradecimentos

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A todas as pessoas que passaram na minha vida e de alguma forma deixaram uma marca.

palavras-chave

Estágio, CRO, Ensaios Clínicos, Investigação Clínica, Monitorização, Biomedicina Farmacêutica, Datamédica

resumo

O presente relatório destina-se a descrever as atividades desenvolvidas no âmbito do estágio curricular que teve lugar na empresa Datamédica, Serviços e Consultoria em Bioestatística, Lda., uma Contract Research Organization (CRO). O estágio teve a duração de 8 meses durante os quais a estagiária desempenhou funções de CRA sendo o principal foco a monitorização dos ensaios clínicos. Para além da principal atividade, foram ainda desenvolvidas funções em áreas adjacentes à investigação clínica, tais como CTA e Medical Writing.

Este trabalho tenta mostrar a visão obtida e os pontos de vista da estagiária enquanto monitora de ensaios clínicos.

Key-words

Estágio, CRO, Ensaios Clínicos, Investigação Clínica, Monitorização, Biomedicina Farmacêutica, Datamédica

abstract

This report intends to describe the activities carried out under the traineeship which took place in the company Datamédica, Biostatistics Services and Consulting, Inc., a Contract Research Organization (CRO). The internship had the duration of 8 months during which the trainee worked as CRA being the main focus the monitoring of clinical trials. Besides the main activity, have also been developed functions adjacent to the clinical research, such as CTA and Medical Writing areas.

This document tries to show the obtained vision and the points of view of the trainee while monitoring clinical trials.

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ABBREVIATIONS LIST

AB – Administration Board

AE – Adverse Event

CAPA – Corrective Actions / Preventive Actions

CEIC – "*Comissão de Ética para a Investigação Clínica*"

CNPD – "*Comissão Nacional de Proteção de Dados*"

CRA – Clinical Research Associate CRF – Case Report Form

CRO – Contract Research Organisation

CV – *Curriculum Vitae*

e-CRF – Electronic Case Report Form

EMA – European Medicines Agency

EU – European Union

IB – Investigator Brochure

ICF – Informed Consent Form

ICH – International Conference of Harmonization

ICH-GCP – International Conference of Harmonization – Good Clinical Practices

IMP – Investigational Medicinal Product

INFARMED – "*Autoridade Nacional do Medicamento e Produtos de Saúde, IP*"

ISF – Investigator Site File

IVRS – Interactive Voice Response System

IWRS – Interactive Web Response System

PD – Pharmacodynamics

PI – Principal Investigator

PK – Pharmacokinetics

R&D – Research and Development

SAE – Severe Adverse Event

SDV – Source Data Verification

SIV – Site Initiation Visit

SOP – Standard Operating Procedure

SSV – Site Selection Visit

TMF – Trial Master File

1. INTRODUCTION

This internship report is an integrant part of a second year Master Degree in Pharmaceutical Medicine and intends to describe the learning outcomes achieved and the activities performed during the curricular training on clinical trials monitoring. The company that has welcomed me was Datamédica, Consultoria e Serviços em Biostatística, Lda., a full service contract research organization (CRO) placed in Lisbon.

From October 2013 to May 2014 it was developed the "on job training" where the main focus was clinical trial monitoring along with several working areas linked to clinical research such as quality management; data management; medical writing and pharmacovigilance. The internship consisted of two different strands of work: the on- site monitoring and the remote monitoring along with other office based activities.

The leading aim of this training report is to describe my experience at Datamédica, Lda., In order to evaluate and appraise the performance during the training, it was settled the following learning outcomes to be accomplished during the internship:

Primary objectives:

- To gain experience on the field of clinical research with expertise in clinical trials monitoring alongside with all the intrinsic competences to work through the clinical trial conduction particularly on the development and regulatory processes;

- To obtain professional experience by integrating a clinical operations team inside the company which will allow to acquire soft skills that are needed to go further on the pharmaceutical industry/work market;

Secondary objectives:

- To consolidate and be able to apply the theoretical knowledge assimilated during the Master's degree;

- To go through the company functional dynamics and understand the business model of pharmaceutical industry;

- To improve the management of interpersonal skills and to strengthen team building and team working skills.

This training report is organized in several chapters chained in a logical manner to ease the access of all:

→ In the first chapter, the introduction, is presented the context and the motivation of this report as well as a brief note about the host institution; it is described the objectives and the structure of the document;
→ In the second chapter, the State of the art, in this chapter the activities that were developed during the training ship are describe and they are divided into two sections, one concerning the specific monitoring training and other related to other clinical research related activities.
→ In the third chapter, On-the-job-monitoring, are described the activities performed during the internship. These activities are separated from the specific training on clinical monitoring and the generic training which contains activities in different areas.
→ In the fourth chapter, the discussion, are evaluated the competences and know-how acquired during the internship;
→ In the fifth and last chapter are made the conclusions about this training report.

1.1. VISION OF THE HOST INSTITUTION

Established on 1996, Datamédica, Lda. counts with over 18 years of experience on the clinical research field. Based in Lisbon, it was funded by a group of people with solid knowledge starting with a strong evidence of biostatistics work. With the aging of the company, the growth was inevitable because it was mandatory reply to the market needs, and so it expanded itself to new areas of research leading to the expertise of clinical trials.

The company is organized by strategic and specialist departments so their employees have autonomy and uniformity of decisions. All employees are carefully selected to be suitable for the working team and able to respond quickly to the needs of the same. The *modus operandi* in which the company is based is on good teamwork and maintaining good interpersonal relationships because without a good individual performance is impossible a good team performance.

As a full service CRO, Datamédica offers a panoply of services during all the stages of drug development such as Pharmacoeconomics; Pharmacoepidemiology; Bioinformatics; Biostatistics; Medical Writing; Quality Management; Pharmacovigilance and, of course, Clinical Trials

Monitoring. These areas also include solutions and partnerships in Regulatory affairs; Product Promotion; Protocol Development and Statistical Analysis. More specifically, inside the clinical development and monitoring, the company is able to perform different and complementary activities: Protocol and Case Report Form (CRF) design, study start-up and site intelligence tasks; study monitoring; study reports and analysis.

The organizational structure allows the company to respond to customer needs due to individualized basis that are treated the solutions for specific shortcomings of the customers.

At the moment the therapeutic areas of research are cardiology, rheumatology, urology, ophthalmology and oncology. The majority of the clinical trials is phase II/III and is mainly in oncology – breast cancer. More lately, Datamédica, Lda. assumed the leading of pharmaceutical market on emergent countries as Angola and Mozambique and recently Brazil. They are on road to be the prevalent health care provider as well as the development of clinical research.(1)

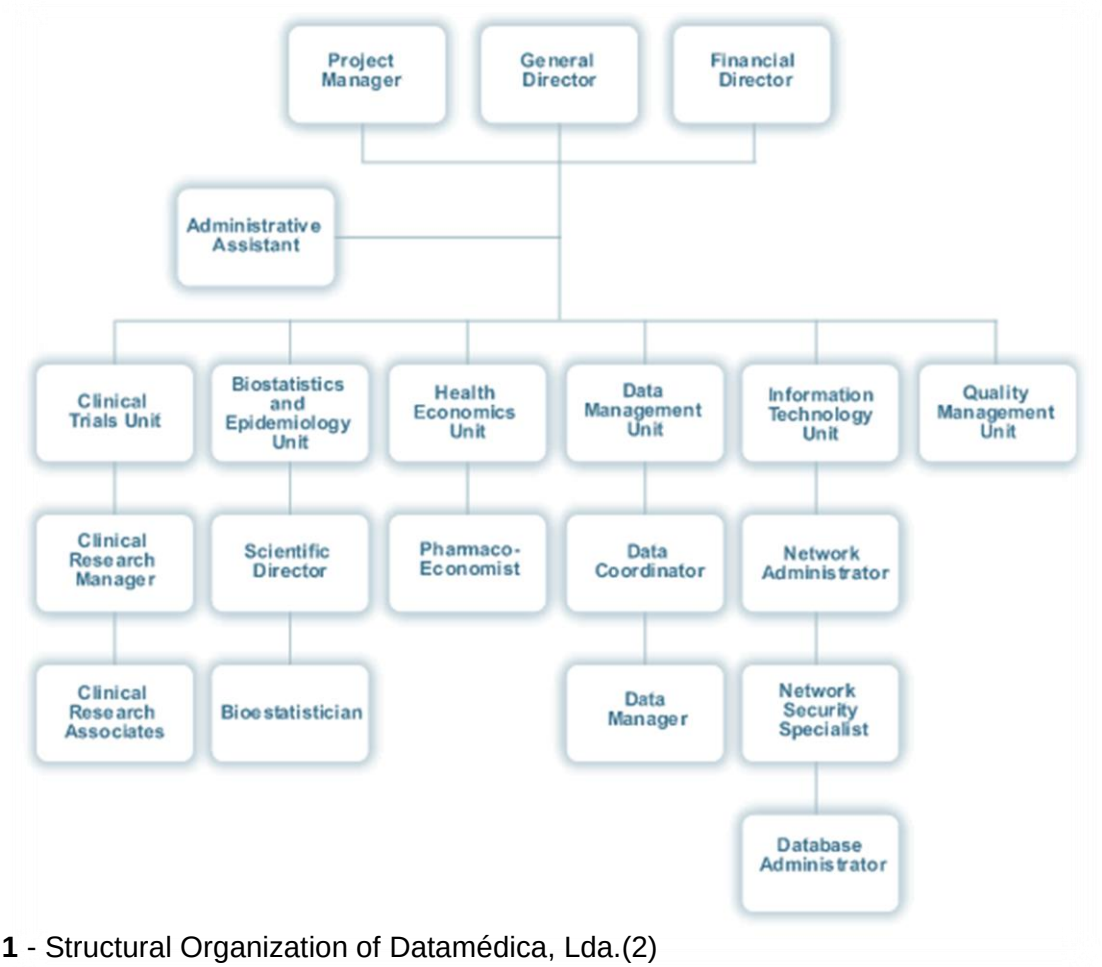

Figure 1 - Structural Organization of Datamédica, Lda.(2)

2. STATE OF THE ART

Clinical trials are a set of procedures in medical research and drug development that are conducted to allow safety (or more specifically, information about adverse drug reactions and adverse effects of treatments) and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols). These trials can take place only after satisfactory information has been gathered on the quality of the non-clinical safety, and Health Authority/Ethics Committee approval is granted in the country where the trial is taking place.(3)

There are different types of trial designs. The parallel design is the most common, is more simple and robust; the duration is less than in other designs; allows straight forward statistical analysis. The Cross-over designs are the second ones more used, are supported by regulatory authorities; the inter-subject variability does not contribute to the error variability. And finally the factorial design, which is less common, are used when is aim to evaluate more than one intervention in a single experiment.(3)

These designs also vary with the stage of development in which it is the drug. The trials can be phase I, II, III or IV (please see figure 2). The type of trial can be determined by considering that pilot studies, pivotal studies (randomized, controlled), and post-marketing studies (registries) are used to achieve different outcomes.(3)(4)

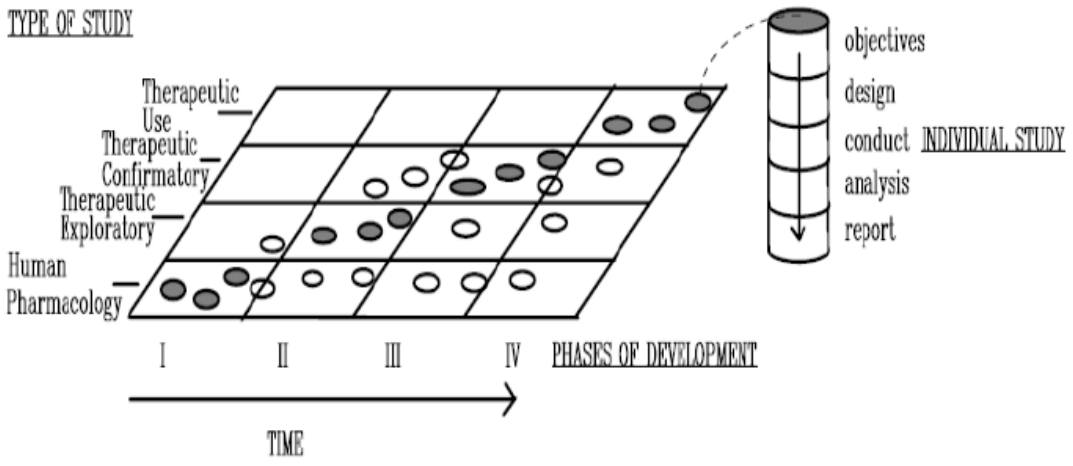

Figure 2 - Correlation between development phases and types of clinical studies.(5)

Obviously the choice of trial design cannot be taken lightly and can be an option too complicated as it is necessary to take into account several factors such as intended statistical analysis; study endpoints; nature of the study; patients target; selection criteria, randomization, blinding/open label procedures, control groups, clinical interventions to be made; estimated duration of the trial (please see figure 3 and 4).(3)(4)

There is still another approach to the study designs which have been increasingly supported by regulatory authorities, which are adaptive design trials. One important characteristic of adaptive design alludes to the prospectively planned changes, that is, the alterations of the trial design are previously planned based on prospectively defined time points within the study so that the existent data would be analyzed and alterations made. There are a number of characteristics that can be changed at the time of the Interim analysis. Sometimes, it can happen that a study modification was a response to an unanticipated event, so not all adaptive modifications are planned.(4)

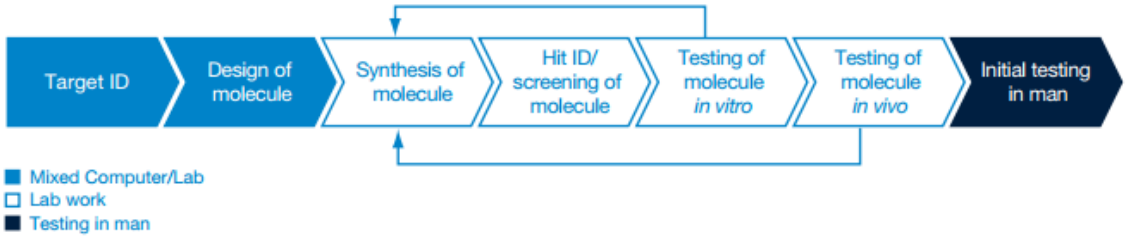

Figure 3 – The current research process.(6)

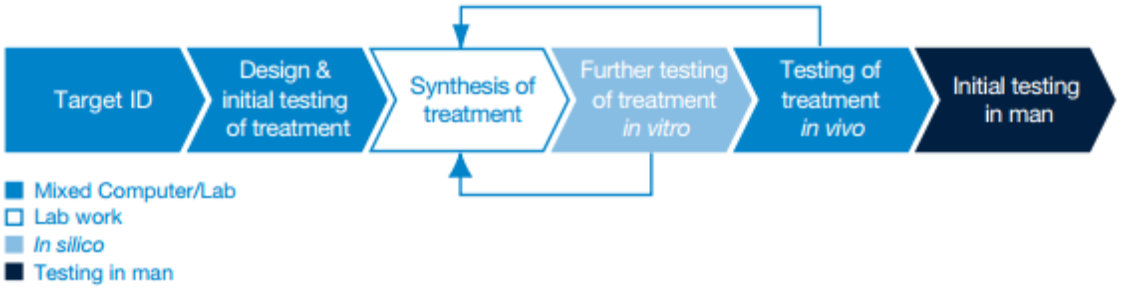

Figure 4 - What the research process might look like in 2020.(6)

2.1. APPLICABLE LEGISLATION AND REGULATORY FRAMEWORK

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 pharmacodynamics 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.”(3)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH - is an exceptional project that was established in 1990. It brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.(7)

The mission aims to create a single set of technical requirements for the registration of new drug products and achieve greater harmonization in the interpretation of guidelines and requirements for product registration, and hence minimize duplication of testing and reporting during the I&D process. It also claims to a better management of human, animal and material use of resources and to streamline the development process maintaining, always, the quality, safety and efficacy of medical products.(8)

This project was created to meet a need that was accurate to have a “golden standard” with regard to the development of new drugs, especially in key aspects of safety, efficacy and quality. These platitudes are essential to make credible and viable medicines, not only in the eyes of the authorities but also to the patients and the entire scientific community.(7)

Therefore, the Pharmaceutical Industry has several reasons to support ICH initiative and its persistent efforts to further harmonize the technical requirements for the registration of innovative drugs. The first one is the reduction of development times and resources by providing guidance and prevents clinical trial duplication. ICH also allows an easier introduction on the market of several countries, especially in ICH regions. This process will simplify inter and intra company globalization since implantation of ICH guidelines, which are recognize as a standard.(9)(10)

Since there are a lot of regulatory procedures of different regulatory authorities to be followed when conducting CT, It is important to point the main aspects to take into account when driving clinical trials. In order to run clinical trials in medical products for human use, the outcome regulatory strategy should be an approximation of all the rules regarding legislation, regulatory and administrative issues, as well as the Good Clinical Practices should be applied.(11)

Before performing a clinical trial, a Clinical Trial Authorization (CTA) should be requested and approved. The first step, even before this submission, is acquiring an EudraCT number. This number is exclusive and will identify the trial, whether it is performed in one or multiple centres. Then the request is submitted to the authorities including already the EudraCT number, the protocol number and information about the pretended clinical trial such as the name of the study and relevant particularities.(11)

Before proceeding to the clinical trial itself, it is mandatory to have an approved authorization by the Ethics Committee. The process could be done before or at the same time as the submission to the authorities. In Portugal, this entity is CEIC (Comissão de Ética para a Investigação Clínica). A requirement is presented to CEIC, which will approve or disapprove the trial, based on the submitted information, on its conception and pertinence, a convenient risk-benefit, among other criteria. The requirement form may be composed by two modules: the first module is common in all the member-estates, and it is the only one requested in Portugal. The decision should be communicated in a maximum of 60 days after the reception of the request. One approval request will be considered valid if it fulfils the specific criteria on the administrative information required, such as the EudraCT confirmation document, the requirement itself, the request form, the investigator's brochure, information on the experimental drug, the summary of product characteristics, and a list of the authorities where the submission was performed. Additional information about eventual special situations should also be present.(12)

In Portugal, specifically, the requirement should be written in Portuguese, and there is a set of specifications regarding the participants, the protocol, the investigational medical product, installations and personnel, and financial subjects.

2.2. CLINICAL RESEARCH IN PORTUGAL

While the picture of crisis is general, Portugal was affected in a very overwhelming way and scenery for clinical research is not the best, principally to conduct clinical trials. According to INFARMED data, over the last 5 years there has been a marked decrease in the number of clinical trials conducted in Portugal.(13)

Table 1 – Decrease of Clinical Trials by phase.(14)

Phase	2007	2011
Phase I	7	6
Phase II	30	19
Phase III	74	58
Phase IV	21	5
Total	132	88

Since 2007 to 2011, the total number of CT submissions decreased from 136 to 88, which corresponds to an approximate 35% reduction on total submissions as showed on table 2. Overall, phase III presents the most volume of clinical trials submissions.(14)

The average decision time performed by INFARMED improved through the years. It started with 45 days of average decision time in 2007 and decreased to 41 in 2011. Further data from INFARMED related to last year, 2012, showed that were 86 clinical trial applications submitted and from those only 76 were approved. So, the landscape for clinical trials in Portugal is getting worse, year after year.(14)

Data from an APIFARMA's study in 2009 showed that Portugal are conducted less 55% CT compared with Belgium, a country with an equivalent dimension. This difference is responsible for a loss of approximately 136 million euro that could be invested in the research units and in the creation of jobs positions in companies and research sites.(13)

It is also important to highlight that the number of trials initiated by academic researchers is decreasing in Portugal, contrary to the European trend.

Table 2 – Decrease of Clinical Trials by phase.(14)

Clinical Trial applications (CTA)	2007	2008	2009	2010	2011
CTA Submitted	136	146	116	107	88
CTA Authorized	131	138	116	105	87
CTA Not Authorized	0	0	0	2	0
Average time for authorization (days)	45	43	42	42	41

Although, in 2013 were evaluated and authorized 116 clinical trial authorization requests, which is an increase of 17 % compared to 2012. As per clinical trial, the average assessment time was 38 days, 5 %, lower than in 2012, with about 99 % of the evaluated processes and concluded fulfilled the statutory period (60 days).(17)

Despite the difficulties mentioned above, there are also some that can play in favor of Portugal and make our country a more attractive place for the clinical trials community. Portugal has lots of professionals willing to enter or remain in the area of clinical research. We, therefore, have a scientific mass considerable to work in this area. Just missing some specific training for people to be made aware of the needs of most clinical trials, but despite this over the years have formed main investigators with some prominence at the time.(15)

Although it is necessary to develop qualified sites, already in Portugal there are some that stand out for their competence and responsibility. With the right investment quickly became sites of excellence that will bring Portugal recognition and competitiveness that so many crave.(15)

Portugal is successful in some therapeutic areas such as oncology, cardiology, neurology and therefore is a unique opportunity to establish sites of excellence in Portugal for these therapeutic areas.(14)

There are very good partnerships between academia and industry that need to be leveraged. The Health Cluster Portugal is a good sample of how partnerships can be developed, and Portugal can be a competitive player in the research, design, development, manufacture and marketing of products and services related to health.(15)

3. ON-THE-JOB TRAINING

Given the urgent need to create professionals and educated workforce for meeting the demands of pharmaceutical industry, the opportunity of an internship drives to a better preparation for those wishing to integrate clinical research.

The traineeship included a junction of several areas of clinical research allowing different experiences what was broadcast in a higher gain of knowledge.

In this chapter I will provide a detailed description of the procedures followed during the internship to perform the requested tasks and activities and introduce the different areas of work. This way, the current chapter is divided in 2 main sections: the specific training and other clinical research related activities. Each subsection is a more detailed description of the activities developed.

3.1. SPECIFIC TRAINING: CLINICAL MONITORING

3.1.1. THE CRA ROLE

Clinical trial monitoring was the main reason that leads this internship to be accomplished within the experience of Datamédica, Lda. It was also the major area of interest and motivation of the trainee.

It was an interesting challenge and intimidating to some extent since it is an area of great importance in clinical research, where much money is invested and bright and overwhelming results are expected. As of high importance for the health of patients, this was one of the main reasons why I decided to embark on this area. The fact that it may be contributing to change for better the health and life of a person means a lot to me. It is also true that scared me a little at first because I did not want and could not have margin for error to be dealing with so important therapeutic areas.

When I was integrated into the clinical investigation department as a CRA trainee, it was allocated to me four Oncology clinical studies in breast cancer and one in Diabetic Retinopathy. When I came across studies in oncology I realized I was not beside a clinical area that would be easy since it would require a lot of me, especially in the knowledge of pathophysiology because only then could follow and understand the protocol of each study. In all of them I assumed functions of CRA and Clinical Trial Assistant – CTA always with the supervision of my Clinical Operations Director.

As part of my integration on the company, the first step was doing a self-training on their standard operating procedures (SOPs), especially on the SOPs related with the Quality and Clinical departments.

The function for which I was trained, CRA, requires and compels to have a very active role in guiding and leading the clinical trial. It has to be the ability of motivate and organize the study team as well as a leading role in planning, coordinating and monitoring all the study procedures. It also is necessary to have a bunch of profile characteristics that are the key to achieve success on managing interpersonal relationships, since all the studies were performed by multicultural and multidisciplinary team members. Essentially, the main focus of the CRA work is checking that the safety of the subjects is paramount; is the main line of communication between the sites and the sponsor; performs site management not only on-site but also from the office (in-house management); review study data from the subjects and verifying it against source data and collecting for processing; Liaising with ethics committee and regulatory authorities, internal departments and suppliers.

3.1.2. SITE START-UP: FEASIBILITY AND SELECTION

Site selection requires that the sponsor can ensure that the trial will take place according to planned; the site has properly qualified professionals; there are enough patients to be recruited to the study; these patients meet the inclusion/exclusion criteria; that study will take place in compliance with the protocol; that the site is able to perform the required clinical assessments.

Clinical trial site selection is important to getting the right data. There are some important considerations to taking on count in site selection, like: qualifications and experience of the principal investigator, study site coordinator and all the research team; suitability of patient population; existence of qualified equipment for diagnostic and therapeutic; feedback from previous trials and historic of recruitment rates; geographic location; Timing of Institutional Review Board meetings Contractual and budgetary negotiations.

3.1.3. SUBMISSION TO COMPETENT AUTHORITIES

To begin the complex process of conducting a clinical trial is necessary to obtain all required documentation by National and European authorities that are legally required to sponsors.

According to the Portuguese Law 21/2014 of April 16th, when a sponsor wants to perform a clinical trial in Portugal it is mandatory to obtain the authorization of INFARMED (Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.) which is the Regulatory Authority in Portugal and the Favorable Opinion from CEIC (Comissão de Ética para a Investigação Clínica) which is the National Ethics Committee for Clinical Research. (16)

The first step to be taken is the request of EudraCT number. This number is a unique identification of the trial in question and must be obtained through the registration in the European Clinical Trials' database. The applicant, who may be the sponsor or his representative, will have to fill out a form with some information about the trial. EudraCT is a large European database that provides the authorities with the necessary information to communicate and oversee clinical trials and drug development. After registration and obtaining EudraCT number, the next step is to create the XML file that is required for study submission to the competent authorities. The XML file, also known as "Annex 1 – Application Form: Request For Authorization 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", is a key point about the whole study because it contains all the information necessary for their identification.

The sponsor is now ready to perform the clinical trial application to the Portuguese Competent Authorities. This application can be made in parallel.

For the submission to INFARMED, the applicant must comply with the information provided by the Authority "Instructions to the Applicants of a Clinical Trial Application" present on his website. In parallel, for the submission to CEIC it is also necessary meet the terms present on the guidance "Instructions to the Applicants for the submission of an opinion request to CEIC". For these two submissions it is important to know that they follow the same line of approval. They undergo through sequential phases: the validation; the additional information request and deliberation phase. The authorities have 30 working days according to the recent law 21/2014 of April 16th to achieve a deliberation about the study. If questions are raised by them at the phase of additional information request, the clock stops and the applicant has 30 working days to reply. Both submissions are made in mixed format: paper and electronic.(16)

Additionally, it is necessary to notify the treatment of data used in the trial to the National Commission for Data Protection (CNPD). For this it is needed to fill a form with the variables that will be collected on personal and clinical data of patients. The CNPD is an independent body with powers of authority, which operates within the

National Assembly. Its generic assignment is to control and supervise the processing of personal data, with strict respect for human rights and fundamental freedoms and guarantees enshrined in the Constitution and the law. The Commission is the National Supervisory Authority for Personal Data. The CNPD cooperates with the supervisory authorities for data protection in other states, especially in defense and exercise of the rights of people living abroad.

To conduct a clinical trial, an authorization request to this organism must be sent, as it needs approval to automatically manage the private data. CNPD will authorize the data management, as long as the following requirements are met:

- The sponsor will not be able to access the data possessed by the investigator that can identify the patients;
- The data should be compiled in a way that their owners cannot be identified;
- At the moment that the owners give their permission to conduct the clinical trials they should also authorize the automatic management of their data and be clearly notified of the purpose and destination of collected files.

During the internship I had the opportunity of being part of three new clinical trial applications for three different studies. I also performed several substantial and non- substantial amendments. It is important to note that every time that is needed to undertake a substantial amendment to the trial is necessary to submit the amendment for approval to the Competent Authorities, which can happen with some frequency since clinical trials are subject to change and adapt to a better design or criteria that benefit patients and research. The main difference between them is that for one to be considering as “substantial” it has to be likely to have significant impact on the patient’s safety, mental and physical integrity or on the scientific value of the study. The substantial amendments that I had performed were made on the scope of a change on the Principal Investigator; the addiction of another study site in Portugal and the addiction of another arm to the study protocol.

Table 3 – Substantial and Non-Substantial amendments requirements.(11)

Substantial	Non-Substantial
▪ Change of main objective of the CT; ▪ Change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the CT; ▪ Addition of a trial arm or placebo group; ▪ Change of IMPs, IMPs dosing or IMPs mode of administration; ▪ Change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment.	▪ Changes to the identification of the trial (change of title, etc.); ▪ The addition/deletion of exploratory/tertiary endpoints; ▪ A minor increase in the duration of the trial (<10% of the overall time of the trial); ▪ Minor clarifications to the protocol; ▪ Correction of typographical errors.

For the submission of substantial amendments to the authorities it is necessary to evaluate which are the documents that are involved on the amendment and then submit the new documents or the new versions with the changes in highlighted format. Then, it is followed the same logic of the clinical trial applications: it is needed to submit in paper format the cover letter; the proof of fee payment (receipt of payment) and the amendment notification form. And in electronic format the changed informative elements; the supportive information changes and the XML file updated (if applicable).

In order to obtain the site's approval for the implementation and execution of a clinical trial it is necessary to make a submission to the Hospital or site Administrative Board Review. The first step is to gather the documents or requirements that are needed and that may depend and vary according to the site. It is also important to understand if this submission can be made in parallel or only after getting the INFARMED's approval and CEIC's favorable opinion, as is requested by several sites.

3.1.4. MONITORING VISITS

According to Law 21/2014, April 16th, the monitoring person (commonly designated by CRA) is responsible for guarantying that the data is correctly and completely recorded and verifies if the storage, distribution and returning of and documentation of the materials under research comply with the good clinical practices. To do this, CRAs perform Source Data Verification (SDV) which is the act of compare the data present in source documents against data registered in the Case Report Forms (CRFs). The sponsor usually defines the number of visits performed during the clinical trial. There are different types of site visits: site selection, initiation, monitoring and close-out.(16)

3.1.4.1. SIV – SITE INITIATION VISITS

The Site Initiation Visit (SIV) is a crucial visit to the development of the study. It is most alike a kick-off meeting of a project because it involves all the "stakeholders" related to them. In this specific scenario, it involves all study team of the site and the necessary representatives of the study: the CRA and sometimes the Clinical Project Manager, Clinical Operations Director and the Medical Director.

During the SIV the CRA performs a clinical trial presentation which must cover the following topics: protocol review; study design; inclusion/exclusion criteria; investigational treatment; schedule procedures and visit assessments; suppliers/vendors involved; GCPs and AE&SAE reporting. This communication serves to ensure that the investigators and study team are aware of their responsibilities and obligations regarding the trial and have the adequate facilities and trained team to do so.

As all site visits, this on needs to be prepared with much anticipation because is essential to have all set-up at the SIV date to initiate the study. So that is necessary to prepare all the folders/binders as the Investigators Site Folder (ISF), the Pharmacy Folder and the Patient Folders; make sure that all supplies (e.g. lab supply; CRFs; exams machines; etc.) will arrive to site on time as well as the Investigational Medicinal Product (IMP). Prior to SIV I needed to fill up and sign a form designed by "Green Light Form" which was the confirmation of the readiness of all trial related procedures that had to be ready for initiation and posterior inclusion of patients.

3.1.4.2. MONITORING VISITS

For the monitoring purpose, all source data must be available for monitoring by the sponsor (or its designees), inspections or audits of Health Authorities. Source data can be defined as all comprised of documents that are the first point of entry of

patient's medical records or certified copies of original handwritten or electronic data.

According to ICH-GCP, source documents are *"original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)"*.(11)

It should be accurate, legible, and up-to-date of patient visits. Each study site should be monitored as early as possible after the first subject has been entered and/or initial data from the study have been received in order to check protocol understanding and compliance with GCP. It is important to note that at the beginning of the trial, the source data should be specified on the Source Data Location Form. Some key points that I learned during SDV performing is that recording the same data in more than one location is not a good practice and should be avoided in order to not create confused and contradicted medical records. Other point to note is that should exist an audit trail every time changes are made to source data. These changes need to be documented by person and date of change.

The monitoring visit activities start before the visit itself, by performing the necessary activities for the visit (preparing documentation, scheduling the visit with the investigational team, assess the recruitment rate, among others).

During the visit I have to ensure that all aspect of the trial are compliant with the protocol, ICH-GCPs and regulatory requirements. The main time of the visit is allocated to eCRF checking and SDV, as mentioned above. It is also necessary to verify the maintenance of ISF and Patient Folders, which involves update documentation if necessary, check the delegation form and the enrollment of new site personnel if so (important to check if they are properly trained before performing any trial-related action).

A visit to the pharmacy should also be done in order to check the specific trial requirements related to IMP. The requirements can be drug stock and supplies; verifying if the IMP are properly labeled and packaged as per protocol; in the case of a double-blind trial assure that emergency code breaks were supplied; IMP dispensing to the correct trial subject; return of IMP from the subject and from the site to the sponsor; check for eventual temperature deviations and security and appropriateness of pharmacy storage facilities. It is also necessary to compare the

IMP accountability forms or records to source documents and ensures that all quantities are controlled and correct. IMP destruction can be made according to site standard procedures or sponsors internal regulations.

At every monitoring visit is important to confirm patient's safety, and to do so is necessary to verify if any Adverse Event (AE) occurred and if it was registered on the eCRF. In case of Serious Adverse Events (SAEs) I need to assure that the event was reported to the pharmacovigillance within 24h.

3.1.4.3. CLOSE-OUT VISITS

The Site close-out visit is performed after the Last patient last visit (LPLV) occurred and SDV was completely done as well as the queries have been answered. Even the sites that have not included any patients need to do site close-out activities. This last visit can occur under different scenarios: can mean that the trial has ended or that the clinical trial site was closed out due to reasons such as elevated number of protocol violations or low recruitment rate which did not justify the expenses on keeping the site open. The visit can also occur after the database lock, depending of the trial.

This visit is prepared by revision of the periodic monitoring reports of the site and by preparing a list of documents to be archived at the investigator file. During the visit I need to ensure that all open monitoring visit issues are closed; collect or schedule the collection of non-medication supplies: unused CRFs, patient diaries or extra protocols, laboratory materials and, if so, equipment loaned to the site during the trial. The most difficult part is the reconciliation of ISF with the correct filled forms and the collection of all relevant documents (e.g. monitoring visit log; drug accountability log; site personnel training log; authorized signature log, etc.). Is necessary inform the Ethics Committee (CEIC) of trial completion.

During the internship I had the opportunity to perform two close-out visits. It was a tiresome experience because I need to fill a lot of "File notes" explaining why some documents were missing and it toke a few hours to get all the essential documents together and prepare the ISF closure.

3.2. OTHER CLINICAL RESEARCH RELATED ACTIVITIES

During my internship at Datamedica I had the opportunity to learn and to explore different areas related to clinical research. These activities are integrated on the cluster of services data the company has to offer for pharmaceutical industry clients. It was very interesting for me take the lead on different areas beside the CRA role but that in a certain way contribute to complement my knowledge of the industry dynamics.

3.2.1. OBSERVATIONAL STUDIES

I had the opportunity of being enrolled on an observational study that was promoted by the Portuguese Society of Nephrology named ODYSSEY study: “observational study on harmonization of practice patterns and clinical outcomes in haemodialysis”. The design of the study was a prospective cohort study based on the collection of observational longitudinal data of all incident patients from a representative and random sample of units in the country. It was a different experience because I went to the haemodialysis units to perform monitoring as well but the scenario of observational studies is a bit different from the interventional ones. I was in charge of collect the patient data and posteriorly do some database entry, which toke me a long period of time. I consider a fruitful experience because I was not aware for the reality of haemodialysis patients and this study will help physicians to select the best treatment approach based on the clinical practice guidelines and outcomes in the future. This study enrolled around 1200 patients from 30 different units distributed in all country and has the duration of 5 years.

3.2.2. 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.

3.2.3. QUALITY AND AUDITS

Quality is a key factor for a good development of clinical trial related activities. If the trial is not based on a good quality system the data cannot be consider accurate and reliable. One of the tasks that I participated in was the reformulation and reorganization of the Standard Operations Procedures (SOPs) and the Quality Manual

review. I also had the opportunity of taking part of an audit from a client. The client was an American Biotech named Puma Biotechnology, Inc., and the purpose of the audit was to verify evaluate if the CRO had the expected requirements to perform the monitoring of the trial in Portugal. This experience was one of my favorites because it was really difficult to make through but very productive and educational. The audit activity started few months earlier because it was necessary to prepare all the documentation, update the internal quality requirements and make sure that all procedures of the trial were followed through the indications of the sponsor. The audit itself last for an entire day, where the auditor, an element of the Global Clinical Trial Team, and two other persons from the sponsor's quality department were present and conducted the audit. At the end of the day we received their feedback and some corrective actions to implement.

4. DISCUSSION

This chapter presents the discussion of the features of the internship activities developed and my point of view of the outcomes and objectives achieved.

Having the opportunity of taking part in a clinical trials team was a pleasing experience, not only because of my professional growth but also because allowed me to face some adversities and learn how to overcome daily obstacles which made me growth individually and personally.

When I first contacted with the clinical trials reality I was very optimistic and excited with the idea of becoming a CRA. I was also a bit nervous with the big responsibility of being in charge of monitoring such difficult procedures and complicated trials, essentially on oncology trials where the patient survival depends on the development and success of the trial. As time passed by and I had more and more contact with the sites and team staff I became more aware of the reality of clinical trials at study sites and the impediments and weaknesses of each one of them and I started to realize that clinical monitoring was not the reality that I idealized initially. There are several factors that can make the site succeed or fail, and that should be taken in account on future site feasibilities.

Several professionals agree that the first and foremost problem shared by clinical trials lies in the choice of sites and inadequate management of the project. In multicenter clinical trials, the study sites begin to screening and randomize patients at different stages, having sites beginning weeks or months later than others. This disagreement is logically connected to an inadequate response to management and may even lead to the recruitment failure. One way to overcome this problem is to choose the sites based on some criteria. Should be given appropriate attention to key operating variables such as recruitment rates and current protocol patient population based on inclusion/exclusion criteria. Is known that every site overestimate the number of patients they can recruit to complete the study. Another point to be checked is the awareness and compliance with GCPs by the principal investigator and all research team, which must be motivated and available to work on the trial.

Another point that I learned how to do was the Financial Agreements between sites and the sponsors. It was probably my biggest challenge during the internship because it is a long and bureaucratic process in which every single detailed of the trial part has to be agreed by each part. It is necessary to be aware of the site

requirements about clinical trial fees, as well as, already available templates the sites may have. It is also important to have input from the investigational team about the distribution of the fees amongst them and, to make sure that all involved parties are contemplated in the agreement (pharmacy, laboratory if needed, the administration board of the site, etc) which means that it is necessary to discuss the contract with all these parties to reach a consensus. Some sites are easier to handle when it comes to contracts since they have few specific requirements and there is a contact person that deals with all contract related activities. But in other cases, the process can take months until is finalized which is another fact contributing to the delay of site initiation.

Despite some tasks that I had performed that were more demanding and despite the shockwave of the reality of clinical trials, I believe that the hard work was necessary and made me grow. And also, I was involved in more positive and excited tasks than negative ones. I enjoyed a lot going to sites and talk with study coordinators and investigators about the trials and known the site's environment that is lived by them. That made me understand more the "other partner" that are the study teams and comprehend better their requirements and their work practices. I realize that the relationship established between the study teams and the CRO/sponsor is an important component to fluidize the process in order to achieve the timelines provided. When relationships are authentic, and based on dedicated trust, when there is collaboration between the parties, the results achieved are better and more predictable. So to increase the motivation of investigators and research teams, it should be more specific the payment of these professionals and should be better established between the sponsor and the administration board for this part would not be lost in the financial contract. It calls for a standardization of financial contracts approved only by one national entity in order to minimize differences and deviations.

Regardless of how much I learnt during my internship, there are some activities that I wish I had done as dealing with Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) on the trials. I think it would prepare me better to future studies, especially on randomization and drug dispensing matters. Other activities that I would like to had done are: dealing with SAEs, working with different types of eCRFs and different sponsor electronic platforms (e.g. e-TMF; Clinical Monitoring Reports platform and study portals, etc.).

During this experience I could always count with the support of my colleagues and my supervisor to motivate me and help me with current doubts. I think we all learnt a

lot with each other and evolve as a working team. My interpersonal skills improved immensely due to a constant need of communication between my team at CRO, with the sites and the sponsors. These last ones were, similarly to study sites, the most challenging communications that I had to done. They don't always understand the Portuguese reality and the problems that we had to overcome to accomplish their deadlines.

I can say that I learn a lot with my own mistakes and became even more independent and autonomous that I already was. My work profiles progressed from a passive and observing point of view towards collaborating leadership. At the end of my internship I shared with my colleagues the feeling of achievement and the sense of work done.

5. CONCLUSION

Overall, I think I achieved the main goal of understanding the CRA role and the dynamics of CRO work environment. Now I can say that I know by experience and not just by theory how it is the lifestyle of a CRA. I can assure that the routine never gets boring because the working days are varied and busy; usually out of the office to the sites for up 2 at 3 days per week and the rest of the days are spent managing the studies from the office. The secondary goals were also fulfilled although the knowledge is a never ending process and I still have some aspects that I need to improve on a daily basis, for example my assertiveness skills and better planning and prioritization tasks. Despite them and at the end of this experience I feel that I had I've grown hugely in comparison with my profile at the beginning.

I am truly grateful at Datamédica for welcomed me and let me be part of their team. Although I am no longer working in the company, I wish them a lot of success and prosperity.

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