



**LILIANA CRISTINA  
SANTOS OLIVEIRA**

**Relatório de Estágio sobre Monitorização de  
Ensaio Clínicos**

**Curricular Training Report about Clinical Trials  
Monitoring**



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Monitoring**

Relatório final de estágio de natureza profissional apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica de Margarida Gonçalves, *Clinical Research Manager* na Datamedica CRO Full Service e do Doutor José Carlos Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro

Curricular training report to be presented to the University of Aveiro to fulfill the necessary requirements for the Masters Degree in Pharmaceutical Biomedicine, held under the scientific guidance of Margarida Gonçalves, Clinical Research Manager at Datamedica CRO Full Service and José Carlos Lopes, Assistant Professor, Department of Physics, University of Aveiro

I dedicate this work to my parents and sister for their patience and constant support in the good and bad moments while writing this report,

“A maior recompensa do nosso trabalho não é o que nos pagam por ele, mas aquilo em que ele nos transforma.”  
(John Ruskin)

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## palavras-chave

Datamedica, *CRO Full Service*, *CRA*, *Medical Writing*, Testes de Legibilidade, Visitas de Monitorização, Astellas Farma Lda, Indústria Farmacêutica e Boas Práticas Clínicas

## resumo

O presente relatório propõe-se a apresentar as atividades desenvolvidas durante um estágio curricular de 10 meses na Datamedica CRO Full Service. A estagiária encontrava-se a desenvolver atividades de monitorização de ensaios clínicos na empresa recetora pelo que este será o principal enfoque deste trabalho. Após 6 meses de estágio curricular, a Astellas Farma Lda subcontratou à Datamedica a estagiária em questão para desempenhar a função de CRA o que permitiu conhecer o mundo dos ensaios clínicos de duas diferentes perspetivas - a das grandes empresas da indústria farmacêutica e a das CROs (empresas subcontratadas pela indústria farmacêutica para desenvolver atividades específicas).

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

Para além da monitorização, foi possível desenvolver outras atividades em outros departamentos da Datamedica, nomeadamente realização de testes de legibilidade e atividades de *medical writing* que serão também apresentadas neste relatório.

Este trabalho encontra-se dividido em dois principais capítulos sendo que o primeiro capítulo pretende situar a empresa de acolhimento na dinâmica da investigação clínica farmacêutica e dar a conhecer o estado da arte dos ensaios clínicos a nível europeu e nacional, com ênfase para a crise na investigação clínica em ambos os níveis. O segundo capítulo constitui a apresentação dos procedimentos que são seguidos em cada área de trabalho desenvolvida durante o período de estágio e a identificação de todas as atividades realizadas pela estagiária. O relatório termina com a discussão e conclusão de todo o trabalho desenvolvido e verificação dos objetivos de aprendizagem definidos no início do estágio.

Todo o trabalho desenvolvido durante o estágio curricular e o contacto com os diversos profissionais envolvidos na área da investigação clínica foram fundamentais para a aquisição de competências sociais e intelectuais que contribuíram para o melhor desempenho da estagiária e a prepararam para o mundo profissional da indústria farmacêutica.

**keywords**

Datamedica, CRO Full Service, CRA, Medical Writing, Readability Tests, Monitoring Visits, Astellas Farma Lda, Pharmaceutical Industry and Good Clinical Practices

**abstract**

This paper intends to present the activities developed during a 10-month internship at Datamedica Full Service CRO. The trainee was developing clinical trial monitoring activities at the host company, which will be the main focus of this report. After 6 months of internship, Astellas Farma Lda subcontracted the trainee from Datamedica to be one of their CRA's, providing her with an opportunity to experience the world of clinical trials from two different perspectives - the major pharmaceutical companies and the CROs (companies subcontracted by the pharmaceutical industry to develop specific activities).

This report tries to show the point of view of the trainee as clinical trial monitor of the two companies.

Besides clinical trial monitoring it was possible to develop different activities from other Datamedica departments such as the realization of readability tests and medical writing activities that will also be presented in this report.

This paper is divided in two main chapters, where the first chapter goal is to place the host company dynamics in the pharmaceutical clinical research environment and provide some knowledge about the clinical trials state of the art nationally and internationally, highlighting the clinical research crisis that is threatening the pharmaceutical world at both levels. The second chapter presents the procedures followed with the different activities performed divided by area of work and the identification/specification of each activity developed by the trainee. The report ends with a discussion and conclusion about the work developed and the verification of the learning outcomes defined at the beginning of the internship.

The work developed during this curricular internship and the contact network developed through the contact with a variety of professionals involved in the clinical research area were essential in the acquisition of social and intellectual skills that contributed to the best performance of the trainee during the internship and prepared her to the professional work environment of the pharmaceutical industry.





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## Abbreviations:

APEL	Astellas Pharma Europe Lda
APIFARMA	<i>Associação Portuguesa da Indústria Farmacêutica</i> (Portuguese Pharmaceutical Industry Association)
CEIC	<i>Comissão de Ética para a Investigação Clínica</i> (Clinical Investigation Ethics Committee)
CNPD	<i>Comissão Nacional de Protecção de Dados</i> (National Data Protection Committee)
COATI	Control, Assessment and Tracking of Therapeutic Investigations
CRA	Clinical Research Associate
CRF	Case Report Form
CRM	Clinical Research Manager
CRO	Contract Research Organization
CT	Clinical Trial
DAM	<i>Direcção de Avaliação de Medicamentos</i> (Drug Evaluation Board)
DART	Data Analysis and Reporting Tool
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
INFARMED	<i>Autoridade Nacional do Medicamento e Produtos de Saúde I.P.</i> (National Authority for Medicines and Health Products)
MHRA	Medicines and Healthcare products Regulatory Agency
NCE	New Chemical Entity
PANDA	Data Analysis Package
PIL	Package Information Leaflet
PSUR	Periodic Safety Update Report
R&D	Research & Development

SME	Small and Medium Enterprises
SRA	Strategic Research Agenda
SOP	Standard Operating Procedures
UEC	<i>Unidade de Ensaaios Clínicos</i> (Clinical Trials Unit)



## Introduction

The present work consists of an internship report developed under the scope of the second year of the Master Degree in Pharmaceutical Biomedicine at University of Aveiro.

From September 2011 to March 2012 it was developed a curricular internship (also called *on the job training*) at Datamedica CRO Full Service, in the Clinical Investigation Department, as a Clinical Research Associate (CRA). The area of expertise in which the internship was focused, was chosen by the trainee and consists on the area she wants to develop a future career in. From March to the present time the trainee was outsourced from Datamedica to a Pharmaceutical Industry Company - Astellas Farma Lda where she has been working as a CRA as well. Therefore, this report will be focused on a 10-month period encompassing the internship period (of 6 months) at Datamedica and 4 months at Astellas Farma.

As a result of this experience this report is being elaborated with the primary aim to describe the trainee's experience at Datamedica CRO Full Service. An insight will also be given about the trainee's job at Astellas. In addition, the present report will demonstrate the new skills, experience and knowledge acquired.

Through the curricular internship the trainee intended to achieve the following learning outcomes:

1. Be introduced to the professional world, by being part of a company staff that allows to perform and specialize in the area chosen to develop a professional career - clinical trials monitoring;
2. Gather know how about how the clinical trials business works and the responsibilities that arise when entering the professional world;
3. Consolidation and application of the theoretical knowledge acquired during the Masters' and the Biomedical Sciences degree;
4. Acquire in depth knowledge related to clinical trial monitoring and develop specific skills required to develop the CRA work;
5. Establish a professional contact network by working in collaboration with other health professionals, such as physicians, pharmacists, other CRA and CRM, among others, whose activities are frequently connected with the CRA work and the conduction of clinical trials;
6. Develop important team work skills and good interpersonal relationships among the companies colleagues and line managers and other professionals that may cross path with the trainee;
7. Get acquainted with the host company functional dynamics;
8. Accomplish all the proposed tasks in a precise, careful and successful way;
9. Resolve situations in the face of adversities;

10. Develop activities not related to clinical trial monitoring but part of the scope of activity of the host company.

These training learning outcomes were defined by the trainee at the beginning of the internship experience. The achievement of these learning outcomes will be discussed in a later chapter.

This report is divided in 4 main chapters.

The first chapter starts with a description of the host company where the internship took part and the company where the trainee got her first job. This section is followed by a clarification of how the pharmaceutical business works - a description of its dynamics - and since the trainee has been developing activities concerning clinical trials, the applied legislation and regulatory authorities will be presented. To conclude this chapter, a small glimpse about the European and Portuguese clinical trials state of the art will be introduced.

The second chapter of this report consists of the methods and results of the internship, that is, a description of how the trainee performed her activities at Datamedica and specifically which activities were performed.

The third chapter focuses on a discussion about the trainee's activities at Datamedica and Astellas where the problems and challenges the trainee went through are evidenced as well as the positive aspects of each activity. Along this chapter the trainee performs an assessment about the achievement of the learning outcomes.

Lastly, the conclusion alludes to the impact these 10 months had in the trainee's growth as a professional worker in the pharmaceutical industry world and her future.

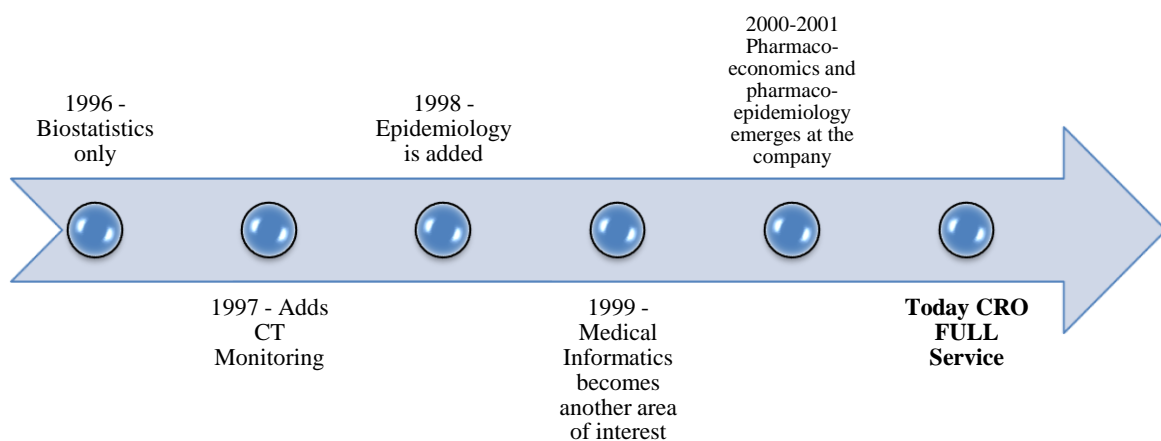


## 1 - The Current Clinical Research Environment

This chapter has as main purpose to provide an overview about the clinical research environment at which the trainee started her on the job training. To achieve this goal, this chapter is divided in 5 sections, starting with the description of the trainee's host company to show its role in clinical research followed by the introduction of the current legislation and authorities regarding clinical trials and ending with the state of the art of clinical trials in Europe and particularly in Portugal.

### 1.1 - Host Company Overview

Datamedica is a CRO (Clinical Research Organization) created in 1996 with the goal of creating a multidisciplinary research company that could support the pharmaceutical industry, universities and other companies dedicated to healthcare research. For 16 years this company has been in the national territory and since its beginning it has had several leaders that gave different purposes to the company. At first it only focused on Biostatistical services but progressively expanded (Figure 1). The environment the trainee experience focused mainly in clinical research, specially conducting CT (Clinical Trials). In more technical words Datamedica is a Full Service CRO whose services encompass “*all phases of the Clinical Trial cycle, including study planning, selection of study centers and investigators, centralized randomization, study monitoring, back-office support and total quality management*”.(1)



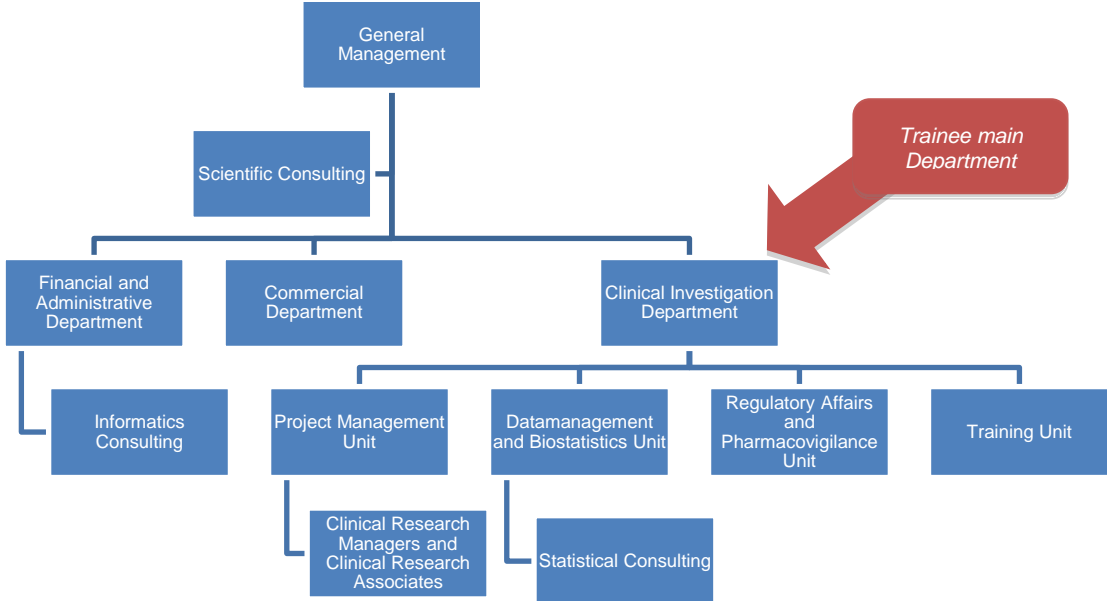
**Figure 1 - Datamedica's evolution through the years** (Adapted from ref. 1)

This is a small company made of only 10 people in house, which made personal interactions with everyone in the company easier to the trainee but working in a small company is different from working in bigger companies because in those companies there is people for each task that needs to be performed. In Datamedica's case, even though everyone has an area of expertise, the trainee needed a multi - task ability, as employees are required to perform all necessary tasks, even if it is

out of their specialization.(2) In the trainee’s opinion this situation was considered an opportunity because it allowed her to get to know other areas of expertise available in the pharmaceutical industry and experience them but on the other hand it required to have very good organizational skills, to know how to prioritize the work activities and to be 100% committed.

The trainee thought the company facilities were very welcoming and adapted to the collaborators needs. Everyone had their own cubicle equipped with a laptop, phone and other necessary/specialized equipment and in addition there was a common space with an enormous desk where, when necessary, the team members can work together. Since the trainee was working as a CRA trainee and due to the frequent need to be in the different clinical trial sites, the company provided a car to the trainee.

Due to its size and high cooperation between its collaborators, there is not a clear limitation of the different departments/units. The trainee was able to identify the department/units of Datamedica with the assistance of Datamedica colleagues and created figure 2. It is important to notice that some of these departments are made up of only one person:



**Figure 2 - Datamedica Organizational Chart** - The areas in red represent the department units at which the trainee performed the internship activities (Adapted from ref. 1)

Datamedica is organized in three different departments: the Financial and Administrative department, the Commercial department and the Clinical Investigation department. The clinical investigation department represents the largest part of Datamedica’s line of work focused on all clinical trials related activities (from clinical trials design, bibliographic research to support the clinical trial, development or revision of clinical trials’ protocol, informed consent and case report form, clinical trial monitoring, statistical analysis and study results publication).

Most of the staff main role in the company is related to Project management, Clinical Research Manager (CRM) and Clinical Research Associate (CRA). The Clinical Investigation unit was where the trainee developed more skills as CRA, by monitoring clinical trials, as pointed out in red in figure 2.

The Data management and Biostatistical unit develops one of Datamedica's most important activities. This unit is responsible for the performance of the statistical analysis of CT, calculation of the sample size for the CT performed at Datamedica, development of statistical reports, among other statistical analysis.

Besides the tasks developed as CRA, the trainee also took part in some activities related to the regulatory affairs unit, performing readability tests. It also assisted in some medical writing work, such as the design of Case Report Forms, clinical trials informed consent, among other tasks, which is a recent expansion of the line of work of Datamedica. The trainee's participation in these units was not as frequent as in the clinical investigation.

The activities developed by the trainee at Datamedica will be described with more detail in chapter 2.

In order to help to successfully perform the core of the CT monitoring, the trainee noticed that there were in place several in-house developed information technology systems: COATI (Control, Assessment and Tracking of Therapeutic Investigations), PANDA (Data Analysis Package) and DART (Data Analysis and Reporting Tool) (Figure 3).(1) These are expert databases of great assistance in handling CT. There was only a small setback on the use of these databases - they were developed a few years ago, and because Datamedica is frequently updating its informatics system and the employees laptops, some of the more recent software's did not run these programs which means they only worked in the oldest computer at the company that is operating at a low speed.

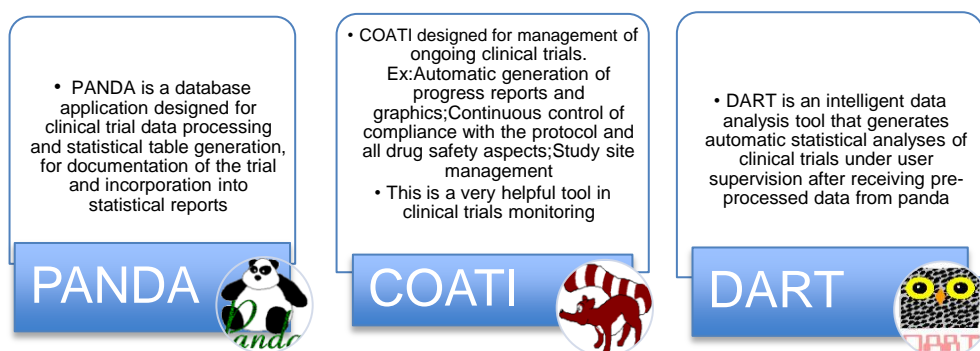


Figure 3 - Datamedica's IT systems (Reproduced from ref. 1)

As a CRO in Portugal, Datamedica has a number of competitors and to keep running it needs to find more clients. In the trainee's opinion this is a difficult task for Datamedica, due to its size and the current crisis situation. However, Datamedica has proven the trainee wrong by welcoming a new general director – Luís Fatela - that explored his professional connections and allowed new people to become aware of Datamedica, and by creating an extension of the company in Angola. These two actions seek the opportunity of growth both in the national and international markets. This was a change in the history of Datamedica that the trainee witnessed and occurred in just a couple of months (see end of chapter 3).

In March 2012 the trainee was outsourced to Astellas Farma, Lda, which has a completely different dynamic when compared to Datamedica. For starters, Astellas is an affiliate of an international pharmaceutical industry company with Astellas Pharma Europe, Ltd (APEL) as the main European House. It is one of the 20 biggest pharmaceutical companies in the world. This is a company that, as it is known today, only exists for 7 years when Yamanouchi and Fujisawa (two major Japanese pharmaceutical companies) fused. In Portugal the roots of Astellas Farma were created in 1967.(2) This company has 21 affiliates throughout Europe and South Africa which by itself shows its size and influence.(2)

This outsourcing situation was only possible because Astellas subcontracted Datamedica, requesting one of its CRAs.

On the opposite from Datamedica, Astellas Portugal is composed of approximately 70 people, distributed by the various departments. The biggest department at Astellas is marketing and sales, due to the fact this company's main goal is to promote and sell its products, but the Medical & Regulatory Affairs department is also one of the most important departments where regulatory affairs, medical advice, pharmacovigilance and clinical investigation are focused. The different departments' limits are very clear and everyone has its work activity very well defined. Some people never communicate with each other because their paths don't cross, so it was difficult for the trainee to keep track on the people working there and to get to know everyone. To help with this situation, Astellas once or twice a year organizes annual meetings with team building activities so that everyone gets to know everyone and to promote team work, effort and interpersonal relationships.

Similarly to Datamedica, Astellas is highly equipped and their collaborators are highly specialized. Each collaborator has to go through training on their Standard Operating Procedures (SOP) and software, and each one has its own laptop, working station, intranet service, telephone, mobile phone and car. The company also has a department specialized in solving the informatics problems, and a human resources department.

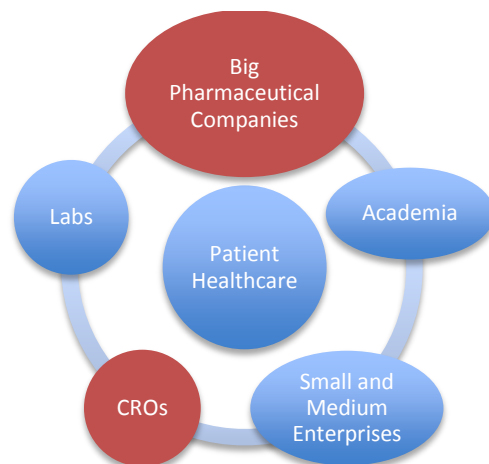
The trainee was part of the Medical & Regulatory Affairs Department, composed of 10 people, and as in Datamedica she was developing CRA activities. The company has highly regulated activities, with department meetings every two weeks in order to keep track of the collaborators work, needs, problems and successes. In addition every collaborator is frequently in contact with the European main house through teleconferences, which was something that did not happen at Datamedica.

Astellas Pharma Europe, Ltd, five main therapeutic areas are: Transplantation, Urology, Dermatology, Anti-infectives and Pain. It is in these areas that this company has been developing its products and has focused its clinical trials.(2) The trainee as an Astellas collaborator had the chance to work with the Urology and Pain therapeutic areas.

These two companies are completely different, especially in size, which allowed the trainee to see how the size of the company influences their work dynamics and how each company performs their activities (see end of chapter 3).

### **1.2 - Clinical Research Stakeholders and Their Role**

Datamedica and Astellas are two types of companies that belong to two different levels in the pharmaceutical industry but share the same main focus: improve patient's healthcare through different extents and activities. They can be called as stakeholders of this industry, and it can be said the trainee was part of two different stakeholders for the last 10 months. Figure 4 emphasizes the main stakeholders in investigational research that revolves around patients and the improvement of its health by providing new medicinal products/devices/procedures and other solutions and each will be discussed in the paragraphs below.



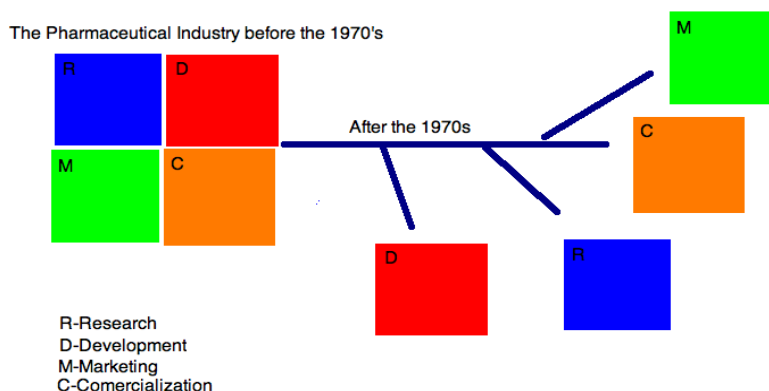
**Figure 4 - The different stakeholders with impact on patient healthcare** – The areas in red represent the stakeholders of the pharmaceutical industry that the trainee was part of

When talking about big pharma companies it is being referred companies such as Roche, GlaxoSmithKline, Astrazeneca and Astellas Pharma among others.(3-5)

These are companies that have resources and capabilities to discover, develop, manufacture and market innovative medicines for major diseases all in the same company. These companies have affiliates around the world and each affiliate most of the times only has one or two of these functions/activities and only the company headquarters gather all these functions.

They all have in common their mission/goal: the improvement of people’s life through the development and introduction of innovative medicines that allow them to live longer, healthier and feel better. To do that, they focus on research and development, by developing the new innovative medicines from the discovery phase to the confirmatory phase (preclinical and clinical development) and commercialization. The difference between them is that each company has specific therapeutic areas so that all together they can provide more innovative medicines that respond to most of the worldwide diseases. For example Astrazeneca, defined cancer, infectious, cardiovascular, respiratory and gastrointestinal diseases as their focus and more than half of the Roche’s projects focus on oncology, inflammation/immunology, virology, neuroscience and metabolic diseases.(3, 5)

In the last decades, instead of the integrated model mentioned above, where the services needed to bring new and innovative medicines to the market were incorporated in the company and their affiliates, it was put in place a new concept that emerged in the 1970’s – service outsourcing that means “to obtain (goods or a service) from an outside or foreign supplier”. This way pharmaceutical industries acquire some services from companies that are specialized in specific services (see figure 5) - Contract Research Organizations (CROs).



**Figure 5 - Representation of the new pharma business model - Outsourcing** (Adapted from ref. 11)

CROs started out to be a “simple fee - for service business”.(6) They allowed to “keep off the burdens and overheads of process management so big pharma can focus on the medical, scientific, and regulatory aspects of drug development”.(7)

The globalization and the economical crisis that has been felt over the last couple of years has been

a major booster on the growth and impact of CROs since they help to reduce the pressure to produce and the costs and time from the pharmaceutical companies. The number of connections between developers and CROs has increased at an elevated rate.(7)

In addition, the range of services contracted has also increased. First, the main services outsourced were mostly pre-clinical and drug discovery services and other single projects (figure 6), however, big pharma are now looking for CROs that can supply entire development programs – *“there's been a shift to more strategic outsourcing where CROs are no longer mere service providers, but full service collaborators (full service CRO)”*.(7)

**Table 1 - Examples of the different CROs types (8-11)**

<b>CRO Type</b>	<b>Service Provided</b>	<b>Example</b>
Full Service CRO	<ul style="list-style-type: none"> <li>•A CRO that provides all the services needed in a clinical research program</li> <li>•One outsourcing process, negotiation and possibly one contract</li> </ul>	Datamedica
Niche CRO	<ul style="list-style-type: none"> <li>•A CRO that specializes in a particular activity/task in the clinical research program</li> <li>•The sponsor has control over outsourcing process and service provider selection</li> </ul>	MEDSOURCE
Academic CRO	<ul style="list-style-type: none"> <li>•<i>“Academic Researchers are the opinion leaders in a disease or experts in a given methodology” (10)</i></li> <li>•<i>“Some academic research centers have determined to offer contract services beyond the traditional sponsor-investigator collaboration” (10)</i></li> </ul>	University of Surrey - Surrey Clinical Research Center

Some experts say CROs are the future of the world of pharmaceuticals. Lately, the major pharmaceutical companies are cutting their personnel as a result of the high difficulties brought by the economic crisis, and these ex-pharmaceutical industries employees find a new job in CROs. The technical skills needed to work in a CRO largely overlap with the ones required in the pharmaceutical industry. This situation is showing how CROs can grow in times like this by benefiting from the experienced personnel and their professional contacts network. This is only bad for early career professionals, such as the trainee, since they have to compete and if they're lucky they will have the chance to learn with these highly experienced professionals.(12) Another proof

of CRO's growth is the current expansion of more Portuguese CRO's to developing countries such as Brazil, Angola, Argentina, Chile, among others. As previously mentioned Datamedica has opened the doors to the international market through its expansion to Angola and it is not the only CRO doing this.

Besides Big Pharma and CROs there are also academic institutions, laboratories and SME's involved in clinical research and focused on the improvement of the global healthcare.

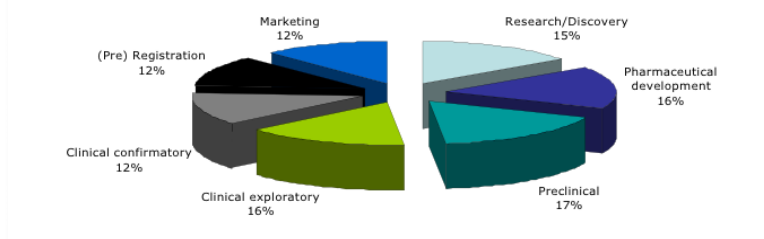
The trainee identified two main roles of academic institutions in clinical research. The first is related to the fact that universities with their research centers provide breakthroughs and innovations (new molecules, genes and biomolecules, disease-specific variables, risk factors, or routes, new innovative technology, etc) to the pharmaceutical industry that can be used in the development of innovative drugs, mainly in the early stage research and clinical trials. However, a gap exists between academia and the pharmaceutical industry, as collaboration between these two stakeholders has not been promoted, especially due to intellectual property and technology transfer issues. But, this is currently being fixed (see section 1.4).(13, 14)The second role of academia is the provision of the right training and education to the current and future professionals. There have been some changes in the way universities provide training and education so that future professionals are *“trained in next-generation techniques, applications, project management, collaboration models, and regulatory science”*.(14)

Small and Medium Enterprises (SME) also provide services in clinical research - they support clinical research and focus on improving patient healthcare. SME *“are independent companies with one or more minority partnerships and with fewer than 50 persons and whose annual turnover or annual balance sheet total does not exceed 10 million euro”*.(15) SME are important for the economy and improve employment but its major problem is in obtaining capital or credit, particularly in the early start-up phase which require access to new technologies or innovation.(15) SME may be subcontracted by pharmaceutical companies or by CROs as they can be specialized in different fields or even in more than one. Figure 6 provides an overview of SME registered in EMA and their specialization.



## SMEs registered with EMA

Phase of development:



**Figure 6 - The phase of development in which SMEs focus** (Reproduced from ref. 16)

Finally there are the laboratories that support clinical research. Laboratories can also be subcontracted by pharmaceutical companies to perform some clinical research activities. Most laboratories that support clinical research are part of the discovery phase of clinical research. In addition there are a number of laboratories that support clinical trials - the so-called central laboratories where blood samples, urine samples and other type of analysis required by specific clinical trials are sent and processed so that the same parameters are applied, which is important in international clinical trials.

These are just some of the main stakeholders in the clinical research environment. The most important message to retain is that they are all interconnected and support each other, especially nowadays.

### **1.3 - Clinical Trials Regulation and Regulatory Authorities**

At this stage, it is important to properly define clinical/investigational research.

For the purpose of this report, investigational research will mainly correspond to clinical trials, since it has been the main area of focus of the trainee for the last year. The present section is going to introduce clinical trials as well as the regulations and regulatory authorities regarding them.

Clinical trials are defined in Directive 2001/20/EC of April 4 as “*any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy*”.(17) This definition shows why clinical trials are so prone to a highly regulated environment: the fact that they involve human subjects whose safety and rights must always be protected. Consequently, there are a

number of laws, guidelines and directives that instruct and advise how to proceed with clinical trials and the subjects involved and several regulatory authorities that are responsible to regulate the way clinical trials should be conducted.

The first that is presented in this report is the European Commission that has an important role when alluding to the requirements to conduct clinical trials in the European Union (EU). It is responsible for publishing EUDRALEX – *“The rules governing medicinal products in the European Union”* which contains all the European legislation applied to the pharmaceutical sector. Volume 10 holds the guidelines applied to clinical trials and has published the main directives<sup>1</sup> approved in the European Parliament.(19, 20) These are:

- Commission Directive 2001/20/EC of *“April 4 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use”*;(19)
- Commission Directive 2005/28/EC of April 8 2005 which further concretizes the previous directive by *“laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products”*;(19)
- Commission Directive 2003/94/EC of October 8 2003 which lays down *“the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use”*;(19)

The most important of these 3 directives is Directive 2001/20/EC, which is usually called as *“The Clinical Trials Directive”*. In Portugal, *Lei n.º 46/2004, de 19 de Agosto* (Law nº 46/2004 of August 19) is the national transposition of directive 2001/20/EC.(21)

Besides the European Commission there are other regulatory authorities that regulate clinical trials both in Europe and Portugal. The European Medicines Agency (EMA), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and INFARMED - *Autoridade Nacional do Medicamentos e Produtos de Saúde I.P.* (National Authority of Medicines and Health Products) are some of them and are going to be further characterized below.

#### European Medicines Agency (EMA) :

EMA is a decentralized body of the European Union and its main goal is to protect and promote human and animal health. It is capable of accomplishing its goal by supervising and evaluating the

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<sup>1</sup> A directive is a legislative act of the EU that lays down the objectives to be achieved by the Member States but it does not define the means to achieve them. The directives recipients may be one or several member states and the national authorities have to adapt their laws to meet the directive goals. (18)

medicines for human and animal use. Its role spans from constant monitoring of the safety of medicines through pharmacovigilance to providing scientific advice and publishing guidelines<sup>2</sup> on quality, safety and efficacy testing requirements that are available for whoever wants to consult them and are additional to the information provided in the EUDRALEX.(22)

#### International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

Before 1990, every country that wanted to market new compounds would have its rules and regulations about what was required to market a new drug. This meant that, to market a compound at an international level it would be necessary to apply the specific procedures of each country where the product would be marketed, which is time consuming and expensive. ICH was the solution to this problem. It is a conference that took place for the first time in April 1990 in Brussels at which the regulatory authorities, industry associations and other representatives of Europe, Japan and the US defined that the interpretation and application of procedures and requirements of safety, quality and efficacy (the three topics based for approving and authorizing new medicinal products) should be harmonized to allow access of new drugs in these three regions more quickly and with simpler procedures (*“reducing or obviating duplication of testing carried out during the research and development of new human medicines”*).(23)

During the last few years, ICH has had an important role mainly reflected on the number of guidelines developed focused on the three topics mentioned above. In addition it has tried to expand its activities and function to other non-ICH regions, to expand the harmonized procedures.

#### INFARMED

The Portuguese national competent authority was created with the intent to *“regulate and supervise the areas of medicinal products for human use, medical devices and cosmetics and body care, according to the highest standards of public health protection, and to ensure health professionals and citizens access to quality, effective and safe medicines, medical devices, cosmetics and hygiene products”*.(24)

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<sup>2</sup> A guideline is a communitarian document mentioned in the legislation as indicated to fulfill a legal obligation in the pharmaceutical legislation or is considered a support document for applicants or marketing authorization holders and/or stakeholders so that they can appropriately fulfill the legal obligations contained in the pharmaceutical legislation. They reflect the most recent and harmonized approach of the scientific knowledge. Most guidelines do not have legal application but they are considered the harmonized position of the Community, which is followed by the pharmaceutical industry stakeholders. Different approaches than the ones defined in the guidelines can be followed if properly justified.

In order to accomplish its aim, this national competent authority needs to regulate and supervise clinical trials, a task that is performed by its unit *Direcção de Avaliação de Medicamentos* (DAM- Drug Evaluation Board) and its subunit *Unidade de Ensaio Clínicos* (UEC - Clinical Trials Unit). It is this specific unit that is responsible for providing all the necessary activities related to the authorization of CT on a medicinal product for human use and substantial amendments to CT already authorized. Also, it guarantees the continuous follow up of CT according to the authorization terms.(24) The other business units with activities related to clinical trials are:

- *Direcção de Gestão de Risco de Medicamentos* (Risk Management Board of Medicinal Products) responsible for monitoring the safety of medicinal products for humans (collecting, register and assessing adverse reactions from clinical trials, periodic safety reports, etc);(24)
- *Direcção de Inspeção e Licenciamento* (Licensing and Inspection Board) which is the unit responsible for good clinical practices inspections related to clinical trials through the subunit of *Unidade de Inspeção* (Inspection Unit).(24)

In Portugal there are two other independent entities that are important to consider when it comes to clinical trials. These are *Comissão de Ética para a Investigação Clínica* (CEIC - Clinical Investigation Ethics Committee) and *Comissão Nacional de Protecção de Dados* (CNPD - National Data Protection Committee), which will be explored below.

### CEIC

CEIC is the national ethics committee for clinical research and it is an independent organization responsible for assuring the rights, safety and well being of the participants in clinical trials. This is accomplished through an assessment of the clinical trial and the procedures to which the participants will be subjected. Before the clinical trial starts, the sponsor of the clinical trial or another applicant selected by the sponsor must submit all the clinical trial elements (clinical trial protocol, the informed consent, insurance, the amount and terms of remuneration of researchers and participants, the investigational team CV's, etc) to CEIC in order to get its ethical opinion.(25) During the clinical trial CEIC closely monitors the trial and must be frequently informed about amendments to the trial that directly relate to the clinical trial subjects.

### CNPD

CNPD is a public institution responsible for controlling and verifying the processing of personal data in order to make sure it is respecting human rights and the constitutional law.(26)

In terms of clinical trials CNPD is responsible for giving an opinion and authorize the personal data processing. The sponsor of the clinical trial must inform CNPD that it is going to be performed a

clinical trial that encompasses personal data processing and with the notification of CNPD it must be provided the documents that relate to the data being processed. (26)

Since there are a lot of regulatory procedures of different regulatory authorities to be followed when conducting CT, in the first weeks of the internship, the trainee was subjected to a training period where the most important legislation related to clinical trials had to be read and understood. The trainee had to go through all these organizations websites to get familiarized with their content and read the most updated legislation and guidelines. The following are the most important:

- Commission Directive 2001/20/EC
- Commission Directive 2005/28/EC
- Commission Directive 2003/94/EC of October 8 2003
- Deliberation N° 333 / 2007 of CNPD *Sobre a protecção de dados pessoais nos ensaios clínicos com medicamentos de uso humano* (About the personal data protection in clinical trials with medicinal products for human use)
- Law no 46/2004: transposition of Directive 2001/20/EC (11);
- Decree-Law no 102/2007: transposition of Directive 2005/28/EC (12);
- Law no 67/ 98 – *Lei da Protecção de Dados Pessoais*
- ICH Efficacy guideline E6 Good Clinical Practice
- ICH Efficacy guideline E8 General considerations for clinical trials

Also, the trainee had to read through CEIC, INFARMED and CNPD considerations about the requirements to get an authorization to perform a clinical trial, to get a favorable opinion of the ethics committee and to notify CNPD when sensible/personal data is going to be assessed.

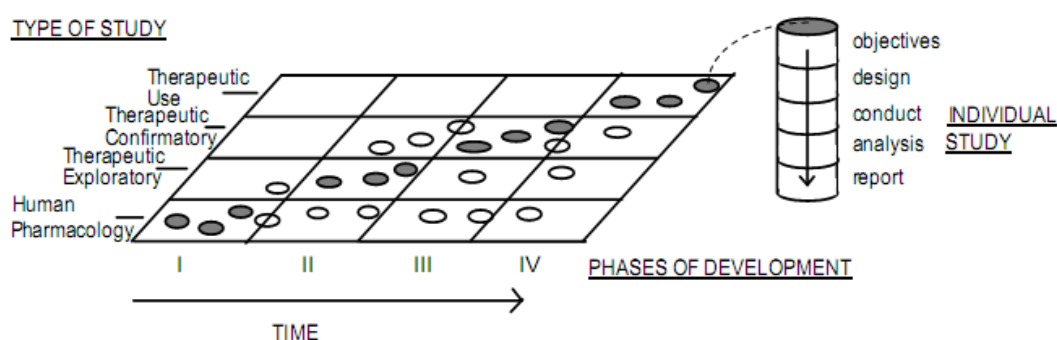
#### **1.4 - Current State of the R&D Process in Europe**

After explaining the definition of clinical trials and the main regulations and regulatory authorities and, before introducing the Portuguese environment concerning clinical trials, a brief glimpse regarding the European state of the art of R&D (Research & Development) in which clinical trials are inserted is of great significance to understand the importance R&D has for the European economics.

In the last decades the R&D process, which culminates in the commercialization of a new drug, has been a logical and sequential process. This process starts with research activities based on a screening process of thousands of compounds to find a compound, called “*the lead compound*”, that shows potential to cure or relieve symptoms of a specific disease. This compound will be the one that goes through the Development process, which is the second part of the R&D process.(27) The current drug development process has been mainly based in trials. First there are the non-

clinical trials that will support the clinical trials of a given scope and duration and give information about the safety of a new pharmaceutical through an animal safety and efficacy evaluation.(28)

With the information acquired from the nonclinical trials, it is possible to start the first administration of the pharmaceutical medicine on humans (First-in-Human clinical trials). The early clinical trials are smaller and determine the initial safety and tolerability of the doses chosen for the new drug. These trials support the latter clinical trials, which are larger and provide confirmatory information about the efficacy of the new drug in the target disease and populations. The information acquired with phase I clinical trials frequently allow modifying the development strategy.(29) Clinical trials are characterized in four temporal phases (Phase I to Phase IV) but this classification has proved to be inaccurate since “one type of clinical trial may occur in several phases” as it can be seen in figure 7. Through the grey circles in figure 7 it is shown which type of trials are more frequently conducted in each phase and shows that the characterization through objectives is more accurate.(29) However, the trainee verified that the most frequently used terminology is still the four temporal phases.

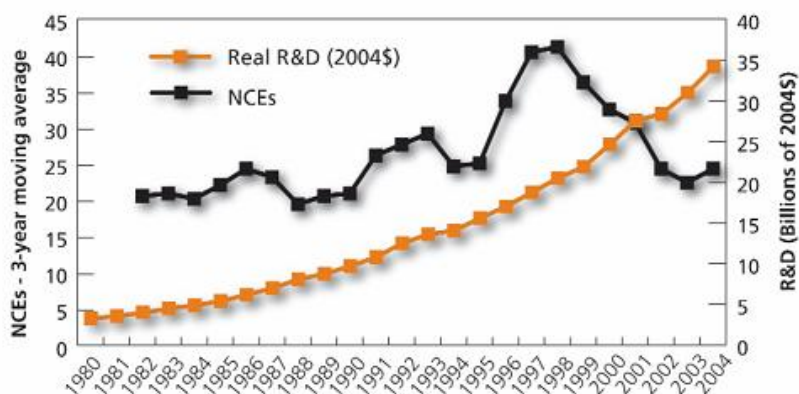


**Figure 7 - Clinical Trials Classification** (Reproduced from ref. 29)

This R&D process has been used for decades and has contributed to the increase in the number of new drugs that have been marketed. This increase in development of new drugs has coincided with the biopharmaceutical industry steadily growth in Europe and its acknowledgment as an important contribution to the European Health and economy.(30)

However, nowadays, this R&D process is currently presenting some setbacks in Europe. It has been verified that in the last 10-15 years there has been a decline in the R&D productivity,(31) mainly due to the fact that the number of new drugs introduced each year has not kept pace with the R&D costs. As it is possible to see in figure 8, even though the costs to bring a new chemical entity has exponentially grown, the number of New Chemical Entities (NCE) has declined substantially.(31) With the current R&D process, it would take, on the year 2000, an average of  $\cong$ 618 Million Euros (802 Million USD) to bring a new drug to the market and the trend has been an

increase in this value.



Source: Tufts CSDD Approved NCE Database; PhRMA

**Figure 8 - Number of new chemical entities that reached the market vs. R&D expenditure (Reproduced from ref. 31)**

Also, there is the fact that quite often the drug, that took 10-12 years to develop, when marketed lacks efficacy and the pharmaceutical companies see all their efforts, money and resources thrown away. This requires a new R&D process that allows to find out which of the lead compounds and drugs aren't going to work when applied to a broader population so that money and time can be saved.(11)

This is the major bottleneck but there are several other characteristics of the R&D process that contribute to this problem and compromise the biopharmaceutical R&D market such as the time it takes to bring a new drug to the market (approximately 12 years). The clinical development phases are the ones where most of the income in the pharmaceutical development is spent, which allows concluding that longer clinical development times drive higher costs and investment in drug candidates. This R&D process has also been associated with elevated attrition rates, which is the failure of a NCE that starts phase I clinical trials to achieve market commercialization. Only 8% of new drugs get approved, the remaining ones fail to achieve approval due to lack of efficacy, clinical safety concerns and toxicological findings.(31)

In addition, some European competitors are currently presenting more attractive market conditions which is causing a relocation of the R&D investments by biopharmaceutical companies to the US and Asia, bringing serious consequences to the European economy and health. "In 1990, major European research-based companies thus spent 73% of their worldwide R&D expenditure on the EU territory, while the figure was only 59% in 1999".(30)

The acknowledgment of this impact has worked as a "Wake up call" to Europe that decided to find a solution to this problem through the collaboration between the stakeholders in the biopharmaceutical business and the creation of the Innovative Medicines Initiative (IMI).(30) IMI's

mission “is to contribute to creating biomedical research and development (R&D) leadership for Europe to benefit patients and society”.(32) “It aims to build and exploit new scientific knowledge and technologies through pan-European Public-Private Collaborations to better enable the discovery and development of new medicines. IMI will make the process of developing new medicines more efficient by conducting research to apply new technologies to drug discovery and development”.(33) This is done through the consensus, participation and contribution of resources, expertise and know-how of the main stakeholders in the pharmaceutical industry, which are: academia, R&D pharmaceutical companies, small and medium enterprises, regulatory authorities and patient organizations.(33)

The areas and activities to be covered by IMI projects are defined in the Strategic Agenda. The first Strategic Research Agenda (SRA) was made in 2008 but was revised in 2011 to address the new challenges and gaps. The first SRA defined four pillars that would be the focus of the IMI activity. The aim was to improve prediction of safety evaluation (early indications of safety problems) and efficacy evaluation (early indication of efficacy by using biomarkers), bridge knowledge management gaps (collaboration to break information barriers) and educational gaps (across preclinical and clinical research and between disciplines).(31) These four pillars were expanded in 2011 to 7 areas of research interest (due to the recent changes in the health systems, pharmaceutical industry and the progress of new science and technology) represented in figure 9.(32)

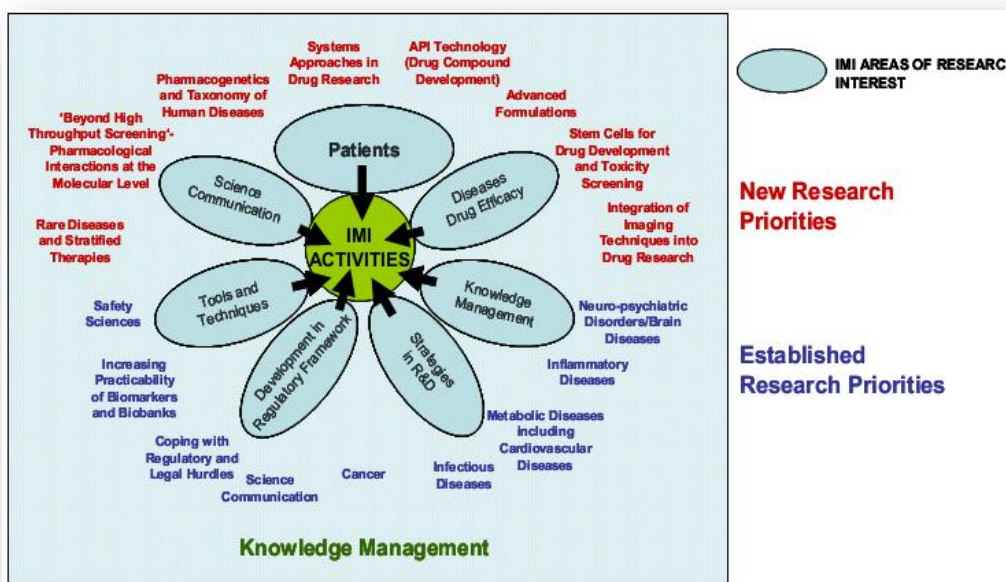


Figure 9 - IMI 7 areas of research interest (Reproduced from ref. 32)

IMI is needed in the European biopharmaceutical industry market but its results will be more relevant on the medium to long term. One thing is for sure - it has been promoting the collaboration



of the variety of stakeholders in this business.

Another different approach that has been gaining supporters is the new R&D process based in personalized medicine. Personalized Medicine means having the right treatment, for the right patient at the right time. This is now being pursued thanks to the major developments in pharmacogenomics and molecular biology that have allowed the identification of the genes responsible for a specific disease characteristic, the response of a person to a given therapy, prediction of a disease outcome, the potential to develop adverse drug events, identifying patients for increased success in CT, etc. This is going to allow giving a specific patient the most suitable drug after identifying his particular type of genetic scheme. Diagnostic methods based on pharmacogenomics are extremely important to achieve personalized medicine. (34, 35) To achieve personalized medicine it is required a high collaboration between basic research (universities), drug developers (big pharma), regulatory authorities and caretakers.(36)

Basically, the one-size-fit all paradigm is being replaced by a new one that meets individual needs. If it is taken into consideration the trainee's experience at Astellas Farma, a big pharma company, it is her opinion that the change from the current paradigm will occur slowly and at least in the next couple of years clinical research will still be based on clinical trials. At least, Astellas is planning for the near future a reasonable number of clinical trials. The main driver for change will be the biomarkers, which are being introduced in the clinical trials for patient recruitment.

### ***1.5 - Performing Clinical Trials in Portugal***

In Portugal, R&D is also an important area of investment. The Portuguese government recognized the pharmaceutical industry sector as a key strategic sector important to the Portuguese economy and growth. Therefore, in the last couple of years R&D has been promoted and as a result R&D and health care spending has increased and clinical research has been strongly stimulated which has been contributing to make Portugal an important pharmaceutical market.(37, 38)

In Portugal there are approximately 130 pharmaceutical companies operating where most of these are multinational companies promoting clinical research.(37)

On the one hand, Portugal has a number of hospitals and universities in major cities (Porto, Lisbon, Coimbra, etc) with experienced personnel (most hospital investigators have conducted clinical trials) to perform and assist clinical trials. It also has a good reputation in what comes to English knowledge of their professionals (either in the pharmaceutical sector or other), which is quite important in this field. Besides the human resources, the hospitals infrastructures are also adequate to the performance of clinical trials (with the availability of facilities such as pharmacy, ethical committee, monitoring room, etc). One important characteristic that has been noticed is the high

patient compliance in clinical trials and the recruitment rates that have been adequate. These features have provided Portugal with a sound reputation conducting clinical trials.(39)

On the other hand, in the year of 2011, INFARMED has only authorized the conduction of 87 new clinical trials in Portugal (figure 10), and according to the European clinical trial register, in portuguese territory, there are being conducted 650 clinical trials (ongoing). If we compare this number to countries similar to Portugal in terms of population numbers, such as Austria and Hungary, it is possible to conclude that Portugal has few clinical trials and that they need to be further promoted (table 2). A higher discrepancy is shown if compared to countries with bigger populations such as Spain, France or Germany (table 2).

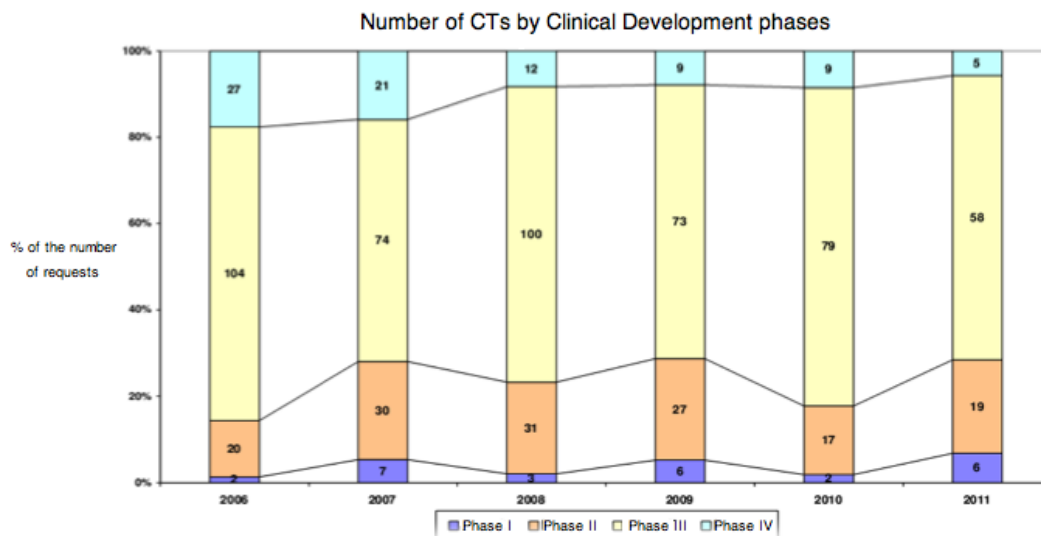
**Table 2 - CT numbers in several European countries** (Reproduced from ref. 40)

Country	Ongoing clinical trials
Portugal	650
Austria	1.050
Hungary	1.684
Spain	4.073
France	2.640
United Kingdom	4.807
Germany	4.308

Most of the clinical trials being conducted in the last 5-6 years in Portugal are phase III clinical trials, whereas phase I clinical trials are less performed (see table 3 and figure 10). In the trainee's opinion this is due to the fact that phase I and II clinical trials require less CT volunteers so it is preferred to conduct this type of CT in high recruitment countries to achieve the recruitment commitment faster. In the case of phase III, since it is needed to confirm the information acquired in previous phases, the number of volunteers necessary is much higher and there is the need for more participating countries and therefore, this is where Portugal is frequently chosen to participate.

**Table 3 - Number of CTs being conducted in Portugal distributed by phases** (Adapted from ref. 40)

Clinical Trial Phase	Clinical trial number
I	4
II	121
III	497
IV	82
Total	650



**Figure 10 - Number of clinical trial authorization requests to INFARMED distributed by phases** (Reproduced from ref. 41)

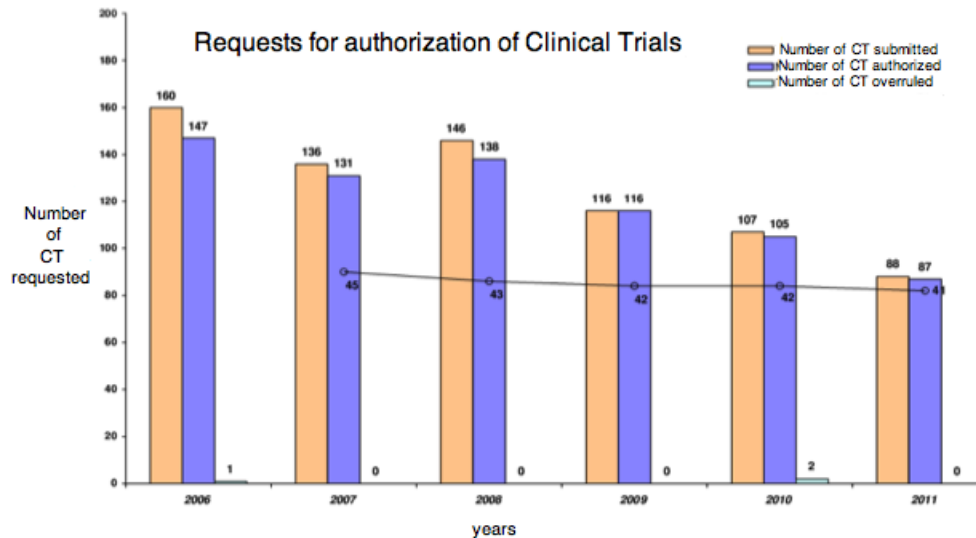
Earlier in January 2012, INFARMED publicly divulged that there were a total of 700.000 participants in the clinical trials ongoing in Portugal. These clinical trials were mainly focused on the oncology area (about 40% of the trials), infectious diseases (about 11%) and neurology conditions (about 11%). Furthermore it mentioned that these clinical trials are being conducted in a total of 90 health institutions. The ones with more clinical trials are university clinical sites, mainly *Hospitais Universidade de Coimbra, Santa Maria (Lisbon) e São João (Porto)* and the oncology institutions located in Porto and Lisbon (*IPO Porto e Lisboa*).<sup>(42)</sup>

The conduction of clinical trials in health institutions regards a number of advantages. The most relevant is the training in clinical research provided to the investigators that take part in the trial, which contributes to the promotion of the use of advanced and new medical practices in the institution. Other advantage has to do with the financial retribution that arises from the conduction of CTs in a specific hospital service. The financial agreement of clinical trials, most times, establishes a financial retribution to the investigators, hospital administration and hospital service where the trial is taking place. This monetary compensation can be used to improve the hospital service with new equipment and better infrastructures.<sup>(42)</sup>

To the participants in CTs, there also are some advantages. In the trainee's personal opinion, the most relevant is the patient's access to new innovative therapies before they are available in the market. This is a major advantage in serious illnesses where the patient has few treatment options. In addition, when participating in a clinical trial the volunteer participant is highly controlled by the investigators, receiving medical care more frequently than if they were not part of a trial. Lastly,

there is the altruistic feeling experienced by these participants since they are contributing to the access to future important treatments.

In spite of the advantages mentioned above, some experts say that the current Portuguese environment does not promote the development of many clinical trials, specially considering non-European countries that have more competitive environments to conduct clinical trials. INFARMED has verified a decrease in the number of CTs authorization requests in the last 5 years, which confirms the statement above (figure 11).

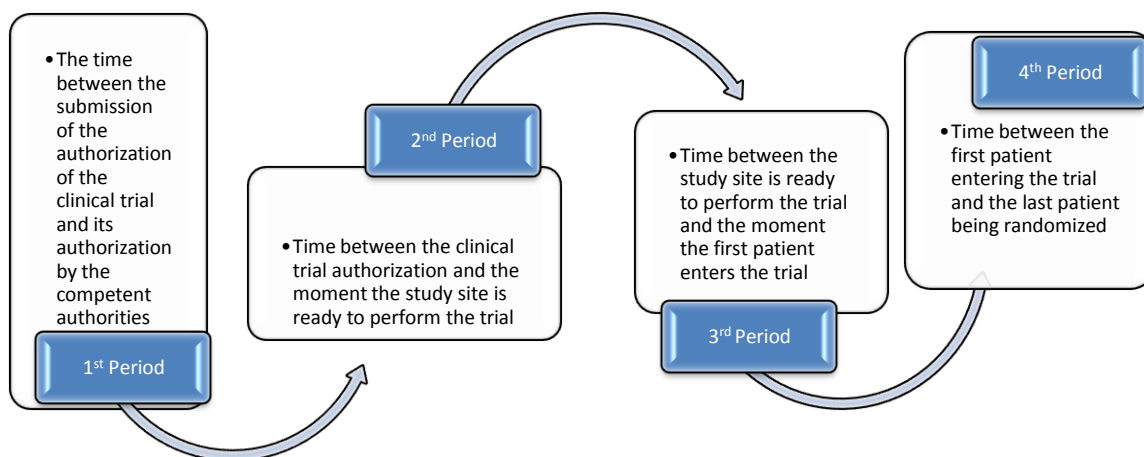


**Figure 11 - Number of requests for clinical trial authorizations to INFARMED** (Reproduced from ref. 41)

Besides INFARMED, some experts also say that the future trend in clinical trials in Portugal is a decrease in the CTs performed. In 2009, a newspaper article, stating the opinion of João Barroca (vice-president of APIFARMA- Portuguese Pharmaceutical Industry Association), said that big pharma are taking CTs outside of Portugal, specially to Eastern Europe and the number of clinical trials in Portugal, even though it should have grown due to the requirement of more clinical trials for each drug, it has stagnated. This article alluded to the delay in the beginning of the recruitment period in several hospitals as the main reason to this trend, especially in hospitals where clinical research is not fully implemented. For instance, in Hospital Santa Maria, this approval process of may only take 15 days after which the recruitment period may start but other hospital may require months.(43) The Chief Executive Officer of the Champalimaud Breast Cancer Unit, Fátima Cardoso, also says big pharma industries are neglecting Portugal. She too, mentions the duration of the approval process as the main cause, but blames INFARMED and CEIC stating they should be faster to give authorization and should apply new legislation with faster approval times. Besides that, she highlights the need for a Portuguese network for sharing information regarding clinical

trials (44) which is being successfully implemented this year (*PNEC, Portal Nacional Ensaio Clínicos – National Portal for Clinical Trials*).

Regarding the clinical trials approval time in Portugal, in 2006, it was made a comparative analysis using as an example an international multicenter phase III clinical trial. This analysis compared the Portuguese approval times with Denmark, Germany and Belgium. It was identified 4 critical time periods (figure 12) and compared between the 4 countries. The results are summarized in table 4.(45)



**Figure 12 - The four critical periods from the submission of the CT to the last patient randomized** (Reproduced from ref. 45, 46)

**Table 4 - The time between critical periods mentioned in figure 12 in 4 different countries** (Reproduced from ref. 45, 46)

Country	Portugal	Denmark	Germany	Belgium
<i>Period</i>	<i>Time (in Days)</i>			
1 <sup>st</sup>	<b>74</b>	22	86	88
2 <sup>nd</sup>	<b>56,9</b>	49,5	14	8,7
3 <sup>rd</sup>	<b>1,53</b>	26,75	9	17,3
4 <sup>th</sup>	95,6	60,3	126	117
Total (days)	228	<b>162</b>	<b>235</b>	231

By analyzing table 4, Portugal is the country that takes more time between the competent authorities submission and the time it takes for the study site to be ready to perform the CT (130,9 days). In this particular point the trainee agrees with the experts mentioned above, the time until approval is critical and if the sponsor is taking part in an European competitive recruitment study it will compromise the countries results. Portugal requires faster timelines to get INFARMED and CEIC approval. On the other hand, after the study site is ready to perform the trial, they seem to

have the fastest first patient recruitment which is quite positive and suggests the clinical research teams are committed to the trials and that Portugal has an adequate recruitment rate.(46)

To sum up and taking into consideration all the gathered information, Portugal seriously needs to create laws or other types of legislation that can guide the process of authorizing clinical trials in the health institutions in which they are going to be performed. On top of that there is the requirement to make the authorization process faster, which also applies to the INFARMED and CEIC.

The decreased number of clinical trials in Portugal is concomitant to the period of the European R&D crisis. It is the trainee's opinion that the current changes at an European level, may contribute to foster the performance of clinical trials in Portugal and change the expert's opinion about the trend of clinical trials in Portugal.

## **2 - Regulatory Affairs & Clinical Research Procedures and Activities**

This chapter is going to focus on the activities developed by the trainee during the last ten months. These were mainly focused on clinical research, even though some Regulatory Affairs activities (Readability Tests) were performed. It is this chapter's aim to provide a description of the procedures followed by the trainee to perform the requested activities and introduce the reader to the developed activities. This way, the current chapter is divided in 3 sections, each related to the main activities developed by the trainee: Readability Tests, Medical Writing Activities and Clinical Trials Monitoring. Each section has two main subsections: the first is the description of the procedure that is usually followed (therefore also followed by the trainee) and the second subsection alludes to which specific activity in the different areas the trainee was responsible for.

### **2.1 - Readability Tests**

The trainee during the Biomedical Sciences Degree acquired some knowledge about the performance of readability tests. At Datamedica, she went through a training period about the readability tests consisting on reading the company SOP, protocols and reports of previous tests conducted at Datamedica. It was the company SOP that taught the procedures mentioned below to the trainee (subsection 2.1.1). Specific data about which readability tests activities the trainee performed is provided in subsection 2.1.2. The point of view of the trainee about the performance of readability tests at Datamedica is given in chapter 3.

#### **2.1.1 - Readability Tests Procedures**

The medicinal products that are marketed in the EU are required to be accompanied by package labeling and package information leaflet (PIL). The labeling is, in many cases, the only information that many people have access to about the use of medicines and they provide essential information about the safe and proper use of medicines. Therefore, it is extremely important that these elements are *“easily legible, clearly comprehensible and indelible”* as mentioned in article 53 of Directive 2001/83/EC.(47)

Furthermore, the same directive defined that the PIL *“shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use”*, that is, it is necessary to perform user testing or readability tests to every medicinal product whose marketing authorization was granted after October 30 2005.(47) User testing is a way of testing the readability of a PIL in a target group. Basically, it is a way of identifying main problems with the PIL and to make sure the information provided is easily and correctly understood without mistakes. It allows the modification of the information, or the way the information is provided, in case there are any “problem areas”. In these tests it is used a full mock-up of the PIL that will be provided after

market approval.

Datamedica's Regulatory Affairs Unit is responsible for conducting Readability Tests in partnership with another company - Pharsolution. In this partnership, Pharsolution is responsible for adjudicating the test of a medicinal product to Datamedica and interacts with the client, and Datamedica performs the following tasks:

- Revision of the package information leaflet;
- Preparation of the readability test protocol;
- Designing readability tests questionnaires;
- Performing readability tests;
- Compilation of the readability test data;
- Preparation of the report of the readability test.

Every time there is the need to perform a readability test Datamedica starts by selecting the team responsible to perform the activities related to the tests.

#### ***2.1.1.1 - Revision of the PIL of a Medicinal Product***

The readability test procedure starts by receiving the PIL of the medicinal product that is applying for a marketing authorization from Pharsolution as well as the methodology of the Readability test to be applied. The PIL's structure and content is revised to make sure there are no misspellings in it. If it is required to alter anything at the leaflet or if Datamedica suggests any change to the PIL Pharsolution is contacted and analyze the proposal with the client to see if he agrees or does not want to make the change.

#### ***2.1.1.2 - Preparation of the Readability Test Protocol***

After the revision of the PIL, the protocol for the readability test of the medicinal product is prepared. The information regarding safety and efficacy information is identified (interactions, contraindications, safety precautions, side effects, etc) and selected for the development of the protocol and the readability test questionnaire.

In the protocol, the medicinal product and its regulatory history (that is, the reason why this medicinal product is taking a user testing) are introduced and the test methodology is drawn based on the indications provided. Pharsolution performs the final revision and the client signs and approves it.

#### ***2.1.1.3 - Designing Readability Tests Questionnaires***

The readability test questionnaire to be used in the PIL user testing interviews is designed at the same time as the protocol and is a protocol attachment.



In the design of the questionnaires, it is crucial to assess the PIL of the medicinal product to find the most important information to be tested and then create questions addressing those issues. At Datamedica the applied questionnaire is divided in two parts. The first part is focused on key questions that reflect issues related to the safe and effective use of the medicinal product and assess the participant's understandability and ability to find the information being asked. This part is usually constituted by 12-15 questions. The complexity of the PIL defines the number of questions. The topics of the questions should not be in the same order as the topics appear in the PIL. It is important to only address one issue per question and these should be open ended, clear and short. In addition the questions formulation should not be equal to what is stated in the PIL, but at the same time should not be too confusing.

The second part of the questionnaire analyzes general characteristics of the PIL, such as the type, size and font, index, amount of information, titles, order of information, type of language, among others, and finishes by asking the participant to classify the PIL of the medicinal product. These characteristics are classified from 1 to 8 where 1 means very bad and 8 very good.

Depending on the marketing authorization procedure<sup>3</sup> the questionnaire may be developed in Portuguese or both English and Portuguese. Pharsolution must also revise the questionnaire.

#### ***2.1.1.4 - Performing Readability Tests***

After the Protocol and the questionnaire have been approved these are printed out in corresponding numbers to the test volunteers needed and, the mock up of the PIL is sent out and printed exactly as it is going to be used after market approval.

The test is composed by a series of face to face, structured sets of interviews where a range of different people need to be able to imagine being in need to use the medicinal product under testing.(47)

The selected people should be representative of the population being treated. People who are directly involved with medicinal products (doctors, pharmacists, nurses, etc) are excluded from the test.

Datamedica recruits the volunteers at Primary care units and pharmacies in the area of Lisbon through the establishment of a collaboration agreement between these institutions and Datamedica. Qualified interviewers randomly invite the patients visiting these primary care units or pharmacies to participate in the test and once accepted they are selected based on the inclusion and exclusion criteria defined for the test. The most important inclusion criteria include volunteers being able to

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<sup>3</sup> If the marketing procedure is national the questionnaire is developed in Portuguese only. If it is decentralized, centralized or mutual recognition procedure the questionnaire will be both in English and Portuguese

read and write, aged 18 or more, and able to understand the test and give informed consent. Volunteers that have participated in previous readability tests, are using the medicinal product under testing or its active substance, are healthcare professionals and/or are employees of Datamedica or Pharsolution are excluded from the participation in the test. These can be more or less specific according to the type of drug being tested, especially if the medicinal product is only used in a certain type of population.

These type of tests are diagnostic tests which means they do not need statistically significant data, only sufficient sample size to identify problems with the PIL.(48)

Before taking the test, the interviewer orally explains the purpose and structure of the test and *“reassures the participants that it is the document that is being tested not them”*.(47) The volunteers must give its informed consent and are given 5 to 15 minutes to read and become familiarized with the PIL before taking the questionnaire.

All volunteers are subjected to the same questionnaire whose questions are orally asked by the interviewer and he/she must answer using his/hers own words. If they are unable to find the correct answer, they must explain why they were not able to find the correct answer. When the requested information is found, the interviewer, through the *“observation of how each participant handled the leaflet and searched for information, noting, for example, whether people become lost or confused”*(47), classifies the degree of difficulty the volunteer went through in a four point scale (4-very easy; 3- easy; 2-some difficulty; 1-Very difficult; 0-Not found) and the time taken by the participant to give the answer.

The number of volunteers that are subjected to the questionnaire will depend on the phases of development of the readability test. Usually there are around 20-27 volunteers divided in two phases: the Development phase and the Implementation phase (Main Test).

The Development phase is composed by the pre-test (3 participants) and the pilot test (3-6 participants)<sup>4</sup>. Both the pre-test and the pilot test have as main objective to test the appropriateness of the questions being tested at the questionnaire, that is, to make sure they will work in practice and to identify major problems with them and correct them before going to the implementation phase. If there is no need to alter the PIL, the test proceeds to the Implementation Phase.

The implementation phase usually involves two rounds of 10 volunteers interviewed by the same interviewer. The objective of these main tests is to get information that the PIL of the medicinal product is clear, legible and easy to understand. The main test rounds will be repeated until the success criteria is met in two consecutive rounds: *“A satisfactory test outcome for the method*

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<sup>4</sup> Usually it is Pharsolution that determines with the client the number of participants in the pre-test and the pilot test or even if there is going to be a pre-test - not all the readability tests have the pre-test.

*outlined above is when the information requested within the package leaflet can be found by 90% of test participants, of whom 90% can show that they understand it. That means to have 16 out of 20 participants able to find the information and answer each question correctly and act appropriately. However, it need not be the same 16 participants in each case. The success criteria will need to be achieved with each question. Results cannot be aggregated”.*(47) If success is not met by the fifth round, the test is stopped and the PIL is deeply revised. It is important to notice that it is only possible to proceed to the next rounds if there is no need to revise the PIL.

#### **2.1.1.5 - Compilation of the Readability Test Data;**

The data acquired from the readability tests are compiled to a spreadsheet that summarizes the results of each participant from their demographic data to the understandability of each question by each participant, the duration taken for each question and the evaluation of the PIL made by the participant. The spreadsheet is also programmed to compile the data in graphs.

#### **2.1.1.6 - Preparation of the Report of the Readability Test**

After data compilation, it is time to make the test report. The final report summarizes the results and concludes whether or not the PIL has a good readability, based on the success criteria. It also indicates the mean overall classification of the PIL attributed by the participants (Very good PIL-average between 7 and 8, Good PIL-between 5 and 6, Bad PIL, between 3 and 4 and very bad PIL average rating between 1 and 2).

The final report analyzes the demographic data that can interfere with the results of the PIL such as the level of education, age group, use of written documents at work and other data about the volunteers.

The report has a section for each test phase and a section of joint analysis of the data of main test 1 and main test 2 (and other rounds if applicable). The data compiled in the spreadsheet is used in this report.

After the report completion, the report is sent to Pharsolution with the spreadsheet and the data from the interviews performed for the test. Pharsolution revises and confirms the results and conclusions achieved, providing the client the entire package.

#### **2.1.2 - Readability Tests Activities Performed by the Trainee**

The trainee took part in several readability tests. In some there was a full participation and in others it was only partial. Table 4 identifies the therapeutic indication/area of the medicinal products that required Readability tests (until March 2012) where the trainee took part, with details regarding the therapeutic formulation and the type of marketing authorization submitted. Due to Confidentiality

issues the medicinal product name, its sponsor and other specific information about the medicinal product are not disclosed. The specific activities developed by the trainee about each medicinal product readability tests are indicated in the last column.

**Table 5 - Readability test activities developed by the trainee**

<b>Therapeutic Area/Indication</b>	<b>Therapeutic Formulation</b>	<b>Regulatory History</b>	<b>Readability Test Activities developed by the trainee</b>
Anesthetic agent (Generic)	Solution for injection	Marketing authorization application through national procedure	<ul style="list-style-type: none"> <li>▪ Revision of the PIL</li> <li>▪ Preparation of the readability test protocol</li> <li>▪ Preparation of the report of the readability test</li> </ul>
General anesthetic/ Sedative (Generic)	Solution for injection	Marketing authorization application through national procedure	<ul style="list-style-type: none"> <li>▪ Preparation of the report of the readability test</li> <li>▪ Compilation of the readability test data;</li> </ul>
Prophylactic therapy for migraines and headaches (Brand Drug)	Capsules	Marketing authorization application through national procedure	<ul style="list-style-type: none"> <li>▪ Revision of the PIL</li> <li>▪ Preparation of the readability test protocol</li> <li>▪ Designing readability test questionnaires</li> <li>▪ Performing readability test interviews</li> <li>▪ Compilation of the readability test data;</li> <li>▪ Preparation of the report of the readability test</li> </ul>
Prevention of bone complications and calcium reduction (Generic)	Concentrate for solution for infusion	Marketing authorization application through decentralized procedure	<ul style="list-style-type: none"> <li>▪ Preparation of the report of the readability test</li> </ul>
Analgesic and anxiolytic (Brand Drug)	Inhalation gas	Marketing authorization application through decentralized procedure	<ul style="list-style-type: none"> <li>▪ Revision of the PIL</li> <li>▪ Preparation of the readability test protocol</li> <li>▪ Designing readability test questionnaires</li> <li>▪ Preparation of the report of the readability Test</li> </ul>

## **2.2 - Medical Writing Activities**

Medical Writing is an integral part of clinical research and revolves around project documents and its activities include documents development, management, review and approval. It is a very important activity in clinical research since the success of a project highly depends on the array of documents that support it at any point of development.(49)

### **2.2.1 - Medical Writing Procedures**

There are a number of activities related to medical writing from designing product development

plans, clinical trial protocols and amendments and other CT related documents (informed consents forms, manuscripts, monitoring plans, among others) to clinical study reports.(49)

Datamedica performs some of those activities when requested by the client but in some cases it outsources medical writing activities, such as the development of some clinical trial protocols. During her internship at Datamedica the trainee had the chance to develop the following Medical Writing Activities:

- Literature reviews for documentation and support of clinical trial projects;
- Design of Case Report Forms;

The procedures followed by the trainee to perform each medical writing activity are described below.

#### ***2.2.1.1 - Literature Reviews to Support Clinical Trial Projects***

The following are the main situations at which Datamedica performs Literature Reviews:

- To support a proposal for a new business opportunity
- To develop a new clinical trial or epidemiological study
- To support a medicinal product file
- To support a clinical trial/epidemiological study document

Most of the literature reviews performed by the trainee emerged after finding a new business opportunity, that required some theoretical knowledge, to support the service to be provided and to convince the client to allow Datamedica to be responsible for the service needed.

The first step in literature review is the realization of a team meeting to prepare the review. If the aim of the literature review is to support a new proposal for a client, this meeting is an opportunity to discuss and brainstorm around what is going to be proposed to the client. The remaining types of literature reviews mentioned only require some background knowledge about what is intended in the literature review, so this meeting works only as a way of providing information and delegating tasks.

The result is usually the definition of the service that will be provided to the client, which is a draft of a design of a clinical trial (either interventional or observational) or an epidemiological study, the draft of a plan of action that resulted in the proposal to the client and the definition of a required literature review that would support some plan of action of the client.

The next step is performing a search through published studies, articles, and/or undergoing or concluded clinical trials. These searches are usually conducted through Pubmed Database or other scientific database or clinical trial databases such as [clinicaltrials.gov](http://clinicaltrials.gov) or [clinicaltrialsregister.eu](http://clinicaltrialsregister.eu).

Following this research, an assessment of the collected data is made and the most relevant data is compiled in a text document.

Trainee's colleagues at Datamedica review the resultant document. They add their input and comments and the required changes are communicated to the author of the document. When no other change needs to be made the document is approved and provided to the client, to be used for the suitable purpose

#### **2.2.1.2 - Design of Case Report Forms**

Lastly, the trainee was also responsible for developing case report forms. Case Report Forms (CRFs) *“are an official clinical data-recording document tool used in a clinical study”* that *“capture data that will be used to evaluate the research questions asked in the protocol and collect adverse event data for safety reports and processes”*.(50) CRFs can also be a way of organizing data in surveys and epidemiological studies.

CRFs are of great significance to the various players in the clinical trial process, since:

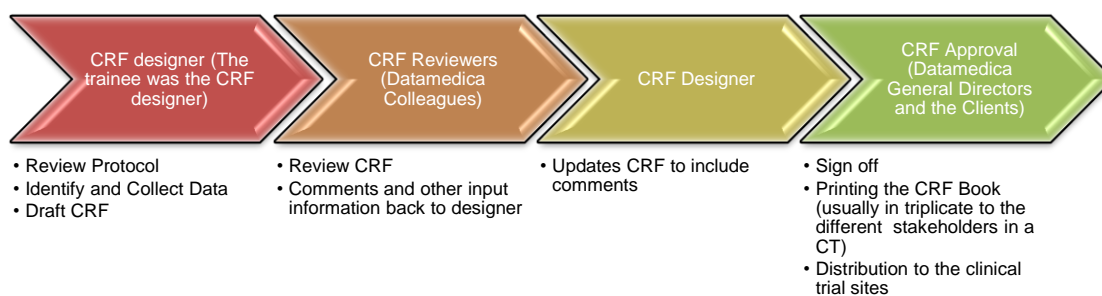
- They help the study site members, specially the investigator to perform a specific evaluation;
- CRA use CRFs to verify if the protocol is being followed correctly and to compare the study data with the source documents;
- Datamanagers and Biostatisticians use them to build database structures, develop and edit checks and to analyze and report the resulted data in the clinical trial report(51)

The clinical trial protocol is very important in the creation of a CRF, since it determines what data should be collected on the CRF. So, the first step is to analyze the clinical trial protocol to determine which data is going to be collected in the trial and the data that should not appear on the CRF.

CRFs, are important data collection tools about the trial and the selection of the information to be collected is critical. Then, this data is usually organized into sections such as: demographic data, vital signs, medical history/physical exam (baseline data), concomitant medication, etc. These are the most frequent modules/sections in CRFs about clinical trials, but each study defines the most appropriate.

Then, there is the adaptation of a CRF template available at Datamedica to the clinical trial/survey/epidemiological study. The selected information is put in the CRF template taking into account that there should be minimal free text responses and most of the information requested should be in the form of questions with multiple choices. It is important to make sure the data is clearly outlined and the questions are concise and simple. To reduce misinterpretation, the developed CRFs are provided with instructions about its fulfillment.

To conclude, it is performed a revision of the resultant CRF by Datamedica’s staff involved in the conduct, monitoring, and analysis or reporting of the trial/survey/study. The CRF design steps are presented in Figure 13.



**Figure 13 - CRFs review process** (Adapted from bibliographic ref. 51)

The trainee witnessed that paper CRFs are being replaced by electronic CRFs, where data is added remotely through personal user access (login and passwords). Datamedica can also provide electronic CRFs if required by the sponsor, but it is necessary to subcontract companies specialized in the application/design of electronic CRF platforms.

### 2.2.2 - Medical Writing Activities Performed by the Trainee

The specific activities developed by the trainee are presented below. Due to confidentiality issues it was not possible to further develop this information.

- Literature Review for documentation and support of clinical trial projects

The information about the literature review projects that the trainee took part is presented in table 6.

**Table 6 - Literature Reviews developed by the trainee**

Project Topic	Objective	Comments
Hemorrhoid Disease	General characterization of the disease and analysis of the impact of a specific medicinal product in its treatment	This literature review was made to support the development of a new indication in hemorrhoids disease of a medicinal product from one of Datamedica’s clients. The created document would be part of the file to be submitted to the competent authorities (INFARMED).
A specific property of coffee constituents	Find the most suitable biomarkers for measuring a specific property of	Literature review for a client proposal to support a possible

	coffee constituents and the biological sample that provided the most accurate measure of the effect being analyzed	epidemiological study
<i>C.Clostridium</i> Infection	General characterization of the infection	Literature review for a client proposal to support a possible epidemiological study
Varicose Veins treatment with a specific type of medicinal product formulation	Find out if there are published studies about the treatment of varicose veins with the required formulation	Analysis of a potential market for a medicinal product of one of Datamedica's clients

#### -Design of Case Report Forms

There were developed two main types of CRFs by the trainee at Datamedica (see table 7). These were paper format CRFs and for both CRFs, the trainee also developed the correspondent instructions about CRF fulfillment.

**Table 7 - Types of CRF with the Trainee Participation**

CRF topic	Objective
Hepatitis	<ul style="list-style-type: none"> <li>▪ Developed for an epidemiology study with the main objective of characterizing the incidence and prevalence of Hepatitis in a specific population</li> <li>▪ CRF designed to help in the organization of the collected information and the resultant report</li> </ul>
Hemorrhoids	<ul style="list-style-type: none"> <li>▪ Developed to provide the client with a “possible” CRF to be used in a clinical trial of a new medicinal product for the treatment of hemorrhoids</li> </ul>

### **2.3 - Monitoring Activities – The CRA Role**

Every clinical trial requires monitoring. According to ICH Good Clinical Practice (see chapter 1 section 1.3 - ICH) monitoring is defined 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 (SOP), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)*”.(52) Through clinical trial monitors (or CRA), who are responsible to perform the monitoring activity, a contact point between the trial sites and the sponsor is established.(52) In this section it is going to be discussed the monitoring activities performed both at Datamedica and Astellas.



### **2.3.1 - Monitoring Procedures**

The main purpose of monitoring is to make sure that:

- The rights and well-being of the human subjects are protected;
- The reported trial data are accurate, complete and verifiable from source documents;
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), GCP and the applicable regulatory requirements.(52)

Both Astellas and Datamedica perform monitoring of clinical trials. This activity is performed by CRAs<sup>5</sup> (such as the trainee) or CRMs. There are a number of activities that comprise monitoring at Datamedica. These are:

1. Document preparation and project revision
2. Sites and investigator selection
3. Clinical trial submission to regulatory authorities
4. Monitoring visits
5. End of trial submission to regulatory authorities

The way these activities are performed usually is described in the SOP of the sponsor of the clinical trial. The sponsor provides Datamedica his SOP and the CRA or CRM goes through a training period focusing on them. Sometimes, it happens that, the sponsor does not provide his SOP and in those situations Datamedica's Monitoring SOP are used to perform monitoring. Since the trainee was also at Astellas Farma Lda, she had a double SOP training period on clinical trial monitoring - the Datamedica training and the Astellas training. Below, there is a general overview of how monitoring was performed by the trainee.

#### **2.3.1.1 - Document Preparation and Project Revision**

As soon as the project is adjudicated the selected CRA/CRM performs a review of the project and analyzes all its documents - Protocol, Monitoring Plan, Informed consent, Case Report Form (CRF), Safety Reporting Plan, Investigator Brochure, etc in order to become familiarized with the trial, the current situation and to prepare the next tasks.

In some situations this revision identifies missing elements to proceed with the trial activities. These missing elements may be important documents that may be asked to the sponsor or in some situations need to be developed in house (if the sponsor does not provide them), which occurred often at Datamedica.

It may be also identified the need to translate to local language important clinical trial documents

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<sup>5</sup> At some companies the CRA is called clinical trial monitor or just monitors, at Datamedica it is used the CRA designation.

such as the protocol synopsis and informed consent form and information sheet, among others. This is a quite frequent activity when talking about international clinical trials. Translations also work the other way around when there is the need to communicate or send clinical trial related documentation to a foreign sponsor. Usually the documents are translated to either English or Spanish.

The next step usually performed is the preparation of the trial files - specially the Trial Master File (or Country File), in order to organize the clinical trial paperwork. In a more advanced state of the trial other files and folders need to be prepared (submission package, site file, investigator file, pharmacy file, etc).

### ***2.3.1.2 - Sites and Investigator Selection***

Clinical trials require the selection of the most appropriate health institutions and health professionals to conduct the trial. To do that, it is prepared a list of potential CT sites that is discussed with the sponsor. Sometimes, the places where to conduct the CT are already selected by the sponsor, so it is only necessary to contact the chosen sites and investigators in order to assess the availability and interest of the investigator/site to perform the trial. This first contact is usually made by telephone or email and as a result of the contact, it is scheduled a date to introduce the trial and provide the possible investigators with some study documents (confidentiality agreement & protocol synopsis). This can be considered the pre-study visit, which allows assessing the logistic capacity of the site to perform the trial (human resources, experience of the investigational team with clinical trials, the number of patients that may enter the trial, the facilities and equipment available at the site...) and discuss some CT requirements. This assessment is complemented by the feasibility questionnaire that is answered by the investigator during or after the visit; At this visit, discussion of some financial aspects of the trial and other specific procedures takes place, and some necessary documents are collected to the clinical trial submission (investigational team Curriculum Vitae, authorization of the chief of service where the trial is being performed, etc) if the site qualifies to perform the trial. Further contacts may be performed to clarify some issues with the investigational team and the site.

### ***2.3.1.3 - Clinical Trial Submission to Regulatory Authorities***

It is part of the monitoring activities the preparation and submission of the trial to the regulatory authorities (see chapter 1, section 1.3). According to the ICH-GCP guidelines and the Portuguese legislation, CEIC and INFARMED need to approve all clinical studies with IMP(s) prior to their initiation.(52, 53) Therefore, it is necessary to submit a request for authorization of a clinical trial to INFARMED and a request for opinion to CEIC. INFARMED and CEIC require the submission

of several documents that will allow to make an assessment/give an opinion about the trial.

The CRA prepares the documentation to submit to these authorities. Frequent contacts with the clinical trial sites and the investigators are necessary to collect the documentation needed from the sites to be submitted. As soon as all the documentation is available it is submitted to these regulatory authorities taking into account the norms, guidelines and instructions available at their websites (see chapter 1, section 1.3). The files are submitted in a CD-ROM and paper format.

This is not the only contact made with the competent authorities in the scope of monitoring. These regulatory authorities may ask for clarifications about the clinical trial while assessing it, which will require the CRA to provide new elements and clarifications. In addition, in case there are substantial alterations<sup>6</sup> to the clinical trial and/or its document these shall be notified to these authorities.(54) Also, yearly, it is submitted Periodic Safety Update Reports (PSURS) to these authorities.

Along with the submission to the regulatory authorities as mentioned above, it is necessary to get the approval of the board of administration and the local ethics committee of the clinical trial site. These two entities must be informed about the decision made by INFARMED and CEIC about the clinical trial application.

Furthermore, it is required to register the clinical trial at the EudraCT database.(55, 56) This is a database of all the interventional clinical trials with medicinal products, which were submitted to the Regulatory Authorities and Ethics Committee, in the European Union. By registering the trial at the EudraCT database, an EudraCT number is attributed to the trial, identifying it. (55, 56)

Lastly, the clinical trial data processing must be notified to CNPD (see chapter 1-section 1.3-CNPD) and thus, registered at CNPD database. This notification is made through an electronic form developed by CNPD.

#### **2.3.1.4 - Monitoring Visits**

The sponsor usually defines the number of visits performed during the clinical trial. There are three types of monitoring visits to each trial site: pre-study visit (explained above), initiation visits, periodic monitoring visits and close out visits. With the exception of the pre-study visit, these visits will be explained below.

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<sup>6</sup> Substantial amendments allude to those that have an impact on the: physical and psychological safety of the clinical trial participants; scientific value of the trial; conduction or management of the trial; Quality and safety of any medicinal product used in the trial.

#### **2.3.1.4.1 - Initiation Visits**

After the authorizations to perform the clinical trial are granted (regulatory green light) and when the necessary conditions to perform the trial at the study site are verified, an initiation visit is performed by the monitors or CRA. This visit is performed to ensure that all investigators, co-investigators, and other study staff members are fully informed about their responsibilities and obligations, concerning a clinical study and are fully prepared to conduct it according to the protocol and ICH-GCP guidelines.

During this visit the pending documentation is collected, the CT protocol is introduced, as well as the Investigator Brochure, the CRF and other clinical trial materials including medication. One important characteristic of this visit is the provision of training about the GCP guidelines and other ICH guidelines. The notification of serious adverse events is explained as well as the informed consent procedure and other important characteristics of the trial.

This visit is performed at each trial site but there may be a meeting organized by the sponsor to give training to (part of) the investigational teams - the Investigators Meeting. This meeting is important especially in international clinical trials. Basically, this visit prepares the sites for the trial and allows the investigational teams to clarify some doubts about the study procedures. Also, it provides the opportunity for the monitor to get to know the investigational team.

After the initiation visit a monitoring report is made and delivered to the sponsor of the trial and a synopsis of the initiation visit is sent to the principal investigator of each study site as well as a list of pending issues that arose from the visit.

#### **2.3.1.4.2 - Periodic Monitoring Visits**

The number of periodic monitoring visits varies according to the type and characteristics of the trial. Usually the sponsor defines this number, but it may require some adjustment as the trial proceeds, especially if the recruitment rate at a specific trial site varies from what was expected, or if there have been a number of issues and protocol violations discovered in previous visits. The number of periodic visits should be specified in the monitoring plan, the protocol, the study contract or the study project.

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. These activities are important to assure the quality of the clinical trial data.

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 monitoring visit the main activity is CRF review and source data verification, meaning checking if the data within the CRF of the trial is in accordance with the source medical documents of the patient. In addition, it is checked if the CRFs are being completed in due time and in full and, if they are accurate, consistent, legible and dated and signed by the investigator. This can only be done after checking if the patient has signed the informed consent form. Besides CRFs, it is important to assess if the trial study drug and materials are being used according to the trial protocol and, if there is the need for more trial materials (the accountability of the material is done). In addition, monitors verify if serious adverse events and other safety information have been correctly notified to Ethics Committee (EC), concerned Regulatory Authorities and to the Sponsor. Moreover, during these visits, the investigator file is updated, the study progress and recruitment rate is discussed, queries are resolved and protocol violations are identified and discussed. It is important that during the periodic monitoring visits the investigational team is available to discuss the issues mentioned above and to correct some errors or missing information on the CRF. After these visits a monitoring report is prepared and sent to the sponsor and another in-house revision of the CRFs is made.

#### **2.3.1.4.3 - Close - Out Visits**

This is the last monitoring visit that is made to a clinical trial site. After this visit the site is closed and the clinical trial is no longer performed at this site. This 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 has to be carried out for all sites that have been initiated, even when no patients were recruited, and is performed in order to guarantee that all investigators, co-investigators, and other study staff members are fully informed about their responsibilities and obligations concerning the archiving of documents, according to the ICH-GCP guidelines. The visits are performed once the last patient has completed the study treatment and all follow-up procedures have been performed and all CRFs have been completed.

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.

This visit usually encompasses the following activities:

- File away documentation at the study sites files (pharmacy file, investigator File, etc);
- Ensure that study data for each patient is complete and accurate;
- Ensure that all adverse event reports are complete and accurate;
- Collecting Signatures and original documentation related to drug accountability, patient screening/enrolment, responsibility log, etc;

- Supplying information about the time study data and material must be kept and informing that there is the possibility of occurrence of inspections or audits or queries resolution after the study site closes
- Preparation of the shipment of clinical trial material to the sponsor

Just like all other monitoring visits it is necessary to elaborate a close - out visit report and a letter of clinical trial site close out.

#### **2.3.1.5 - End of Trial Submission to Regulatory Authorities**

The sponsor is the entity responsible for determining when the clinical trial ends. Sometimes a premature termination may occur, which is decided either by the sponsor or the regulatory authorities.

The clinical trial is considered finished when the clinical trial ended in all the national sites. After all the clinical trial sites are closed out, there are only few activities to be performed in order to consider the clinical trial as finished.

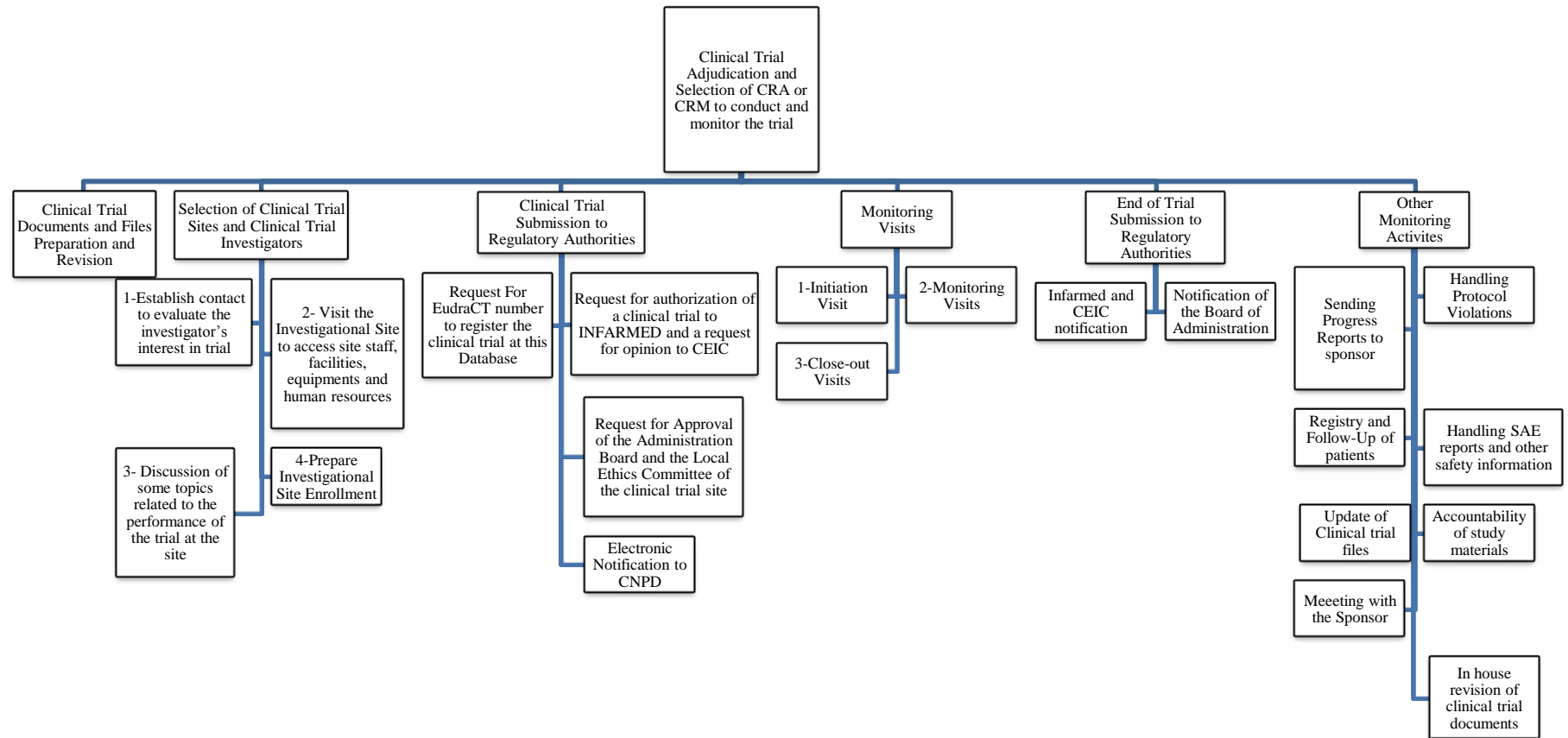
The end of the trial must be notified to the regulatory authorities (INFARMED and CEIC), to the board of administration and the ethics committee of the clinical trial site. (54)

In addition, it is necessary to return to the sponsor all the study material, which includes the used and unused medication, the files, and the CRF pages, among others.

Apart from what has been explained, the CRA performs other essential activities to managing clinical trials such as the frequent progress reports to the sponsor, the registry and follow up of the patients that are part of the trial, in house revision of the clinical trial documents and safety information (Serious Adverse Events reports sent by the investigator), update of the Trial files, accountability of study materials, meetings with the sponsor, among others. These tasks are outlined in Figure 14, along with most of the above-described activities.

Such other activities that the trainee performed during these last 10 months, a training period was required, that consisted on reading the company clinical research SOP, the ICH-GCP, the CEIC and INFARMED instructions related to clinical trials, the CNPD orientations and the applied legislation.

#### **Figure 14 - Clinical Trial Monitoring Activities**



### **2.3.2 - Monitoring Activities Performed by the Trainee**

As mentioned in section 2.3.1, in the present section it will be described the Clinical Trials that the trainee took part both at Datamedica and Astellas Farma Lda described in the same order. Each trial will be briefly characterized and the main trial related activities performed by the trainee are going to be presented.

It is important to mention that most of the CTs described below are interventional clinical trials and only one is an observational study.

- Phase IV CT in the neurology therapeutic area

This CT concerns a neurological condition (acute ischemic stroke) with a Spanish company as a sponsor, and performed in Spain, Germany and Portugal. It had as main objective the determination of the effect of a new compound in comparison with placebo, and was multicenter, prospective, double - blind, randomized and controlled study. In Portugal there were eight clinical trial sites.

Each study subject in this study had five study visits during a period of 12 weeks and was administered two different formulations of either the study drug (IV and oral) or placebo.

In this CT the trainee role focused on conducting monitoring visits to the sites. The trainee performed five monitoring visits on three different clinical trial sites.

- Phase IV CT in the Renal Transplantation Therapeutic Area

This CT was designed to comply with requirements of the United Kingdom Regulatory Authority (Medicines and Healthcare products Regulatory Agency (MHRA)) due to the fact the medicinal product under investigation is a generic drug product, that requires the performance of CT to demonstrate clinical safety and efficacy profiles similar to the brand product. In this particular case it was defined as efficacy endpoint the number of renal transplant efficacy failures in order to establish non-inferiority of this drug compared to the brand product.

A pharmaceutical company in Brazil sponsored this clinical trial and it was performed both in Portugal and Spain. It had an uncommon design methodology, since it was designed to spare renal transplant patients to a CT, so there weren't many changes to the common clinical practice introduced by the protocol. It was a multicenter, open label trial with historical controls<sup>7</sup>. The number of patients to be recruited to this CT was 250 for each group (500 total). The eligible patients were only subjected to three study visits (baseline visit, mid-study and final visit) during a six months period. It was supposed to be performed in six clinical trial sites but this number was

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<sup>7</sup> It has two cohorts - prospective cohort and retrospective cohort (historical control group-patients that were treated with the brand drug product)



reduced to two sites since the medicinal product under study was already on the market for several years and there are already some better options to it. Therefore, few hospitals still use it.

This trial was at the start-up phase when the trainee arrived at Datamedica and so, the activities performed were:

- ✓ Clinical Trial Documents and Files Preparation and Revision
- ✓ Selection of Clinical Trial Sites and Clinical Trial Investigators
- ✓ Clinical Trial Submission to Regulatory Authorities

- Phase IV CT in the Rheumatology Therapeutic Area

Another Phase IV CT, in which the trainee took part, was a trial with the main objective to collect data regarding safety, efficacy and tolerability of a new dosage form of a medicinal product that combined two active substances. In order to accomplish that, the trial was a double blind randomized clinical trial with a four parallel treatment group. The four treatment groups were: the active substances individually in the doses already commercially available, versus the combined drug in the dose already marketed and the new dosage form. The efficacy assessment was based on a questionnaire that would evaluate the improvement of the condition under study.

The recruitment aim of this clinical trial was 480 subjects (120 for each treatment arm) and they would only be part of the study for 14 to 21 days. They would only be exposed to the medicinal product during 7 days. The clinical trial patients would be recruited during a 12-month period.

This was a national CT sponsored by an Italian pharmaceutical company that has a Portuguese affiliate (see chapter 1- subsection 2). This clinical trial will have six clinical trial sites.

This trial is similar to the previously described due to the fact that when the trainee first arrived at Datamedica it hadn't started as well and so the activities performed for this trial were similar to the ones mentioned above:

- ✓ Clinical Trial Documents Preparation and Revision and Files Preparation
- ✓ Selection of Clinical Trial Sites and Clinical Trial Investigators
- ✓ Clinical Trial Submission to Regulatory Authorities

- Phase II CT with a medical device to be applied to the Cardiology Therapeutic Area

The trial about to be described has an interesting and different feature when compared to the previous ones since it focus on a medical device. The main difference from the procedures described on chapter 2 section 2.3, subsection 2.3.1.3, focus on the fact CEIC does not need to approve this type of trial. The other procedures are all the same and the trainee participated mostly on the clinical trial submission to regulatory authorities and documents preparation.

The CTs that will be described from this point on are the ones monitored at Astellas Farma. There were three trials that were monitored by the trainee and the European headquarters of Astellas (APEL) sponsored them all. These CTs focus on products developed by the company.

- Phase III CT in the Urology Therapeutic Area

The first Astellas trial being described alludes to the usage of a new product in the urology area, specifically in overactive bladder. The main objective of this trial was to assess the clinical efficacy of a new product in patients that were not satisfied with the therapeutic offer that was on the market. In order to achieve this primary objective the trial had the following design: international, double blind, multicenter, parallel group, with two treatment groups. One of the treatment groups was the new product and the other treatment group was a product of common therapeutic use in the treatment of overactive bladder. There were 36 countries participating in this trial in order to achieve a recruitment goal of 1992 subjects in just seven months of recruitment. In Portugal the trial had six sites with a recruitment commitment of six patients each. Each subject goes through five study visits in a period of 14 weeks.

The trainee went through most of the trial life cycle, from submission, initiation and monitoring and so, a set of different activities were developed:

- ✓ Clinical Trial documents preparation and revision (including clinical trial agreements, financial agreements preparation and clinical trial insurance requests)
- ✓ Pre-study visits (feasibility visits)
- ✓ Clinical Trial submission to regulatory authorities
- ✓ Attending monitoring and investigators meeting
- ✓ Clinical trial submission to the clinical trial sites
- ✓ Performing initiation visits
- ✓ Performing monitoring visits

- Phase IV CT in the Urology treatment area

Besides the CT above, the trainee also monitored another trial in the urology treatment area. This CT studies another product of Astellas but in patients with locally advanced prostate cancer. This trial compared two types of therapy with the same product in those patients. In terms of design this trial is also an international CT, multicenter, randomized, open-label and had as objective the inclusion of 700 subjects that have to go through two trial periods - the treatment period and the follow-up period.

When the trainee arrived at Astellas Farma the trial was already going on since 2006 and had just finished the treatment period in the five clinical trial sites. This also meant that the sponsor wanted

to go through soft and hard database lock, which means, the need to solve all treatment period queries. This was the main activity conducted by the trainee while monitoring this trial. In addition, this study had a follow up period every six months after the treatment has finished, that required the need to contact the study subjects to see if they were still alive and so, the trainee had to keep track of these contacts informing the sites when it was time to contact the patient and if they did it indeed.

- Observational study in the Pain treatment area

The last study that was monitored by the trainee was not an interventional study. It was an observational study that analyzed the use in common clinical practice of an Astellas Product in the pain treatment area. This was a study conducted at an European level and multicenter. The main objectives were to assess the efficacy of their product in clinical practice and assess the time to retreatment with their product. The number of target subjects that would be treated with their product and assessed as part of the study was 1200 subjects.

As an observational study the main activity that needs to be conducted by the sites, is the selection of the study subjects and collection of the information at specific timelines required by the trial. In Portugal there are 10 sites performing the study.

This study experienced an interruption period that was imposed due to the need to clarify some issues with CEIC. The trainee was one of the Astellas' team members that contributed to the "unblocking" actions required, as well as other activities that made the study evolve:

- ✓ Pre-study visits (Feasibility visits)
- ✓ Clinical trial Submission to the Clinical Trial Sites
- ✓ Performing Initiation Visits
- ✓ Performing Monitoring Visits



### **3 - Discussion**

This chapter presents the discussion of the aspects of the internship activities most positive or critical to the trainee, as well as, her opinion about them. In addition this chapter is also a reflection about the work experience acquired during the 10 months of the on the job training/internship.

Ever since the first day of the internship the trainee became part of a new environment - the pharmaceutical world - working environment. It was one of the trainee's goals to be introduced to the professional world as a CRA of the pharmaceutical world and Datamedica by choosing her to be part of the clinical investigation unit staff rapidly contribute to the achievement of the trainee's goal (learning outcome 1 at this report introduction). It was at Datamedica that the trainee really got to know what were clinical trials, its importance to the pharmaceutical research world and most importantly, became aware of the different perspectives regarding clinical research - the perspective of the sponsor, the perspective of the investigator and the perspective of the contracted company that performed the trial. In a few words, the trainee fulfilled her learning outcome 2 of gathering know how about the CTs world. Moreover, Datamedica permitted and supported the trainee's outsourcing to Astellas to gain more experience in a different pharmaceutical world environment but still as a CRA. Being a CRA is a huge challenge, everyday there is an activity that makes the trainee defy herself to perform it or solve it.

As it was possible to see in the previous chapters of this report, even though the trainee was chosen to perform CRA activities at Datamedica, this CRO allowed her to experience other activities, which are directly linked to the achievement of learning outcome 10.

Besides monitoring, one of the most frequent activities developed by the trainee, was the performance of readability tests procedures. As already discussed on section 2.1.2, the trainee was most frequently responsible for the development of the readability tests' protocol and report. These two activities were not difficult, since they only required adaptation of a template-document already developed by Datamedica for each medicinal product. The report required more attention than the protocol design, because it needed an assessment of the graphics acquired after the user testing of the PIL, to reach a conclusion whether or not the PIL is readable. As the trainee gained practice creating the test protocol and report, she quickly realized which were the critical sections that required more focus and the activity became accessible to perform.

The design of the questionnaire for the readability testing interviews and performance of the readability testing interviews was much more challenging. The difficult part was formulating the questions, because the answer could not be too straightforward to the volunteer, and at the same time could not confuse him. Also, in some PILs the important information was insufficient to create the 12 questions defined as a minimum and attention was necessary to neither formulate

irrelevant questions nor repeat information. On the opposite, there were PILs with too much information, which made the selection of these issues difficult, especially since it is important not to make the questionnaire too long, so that the volunteers don't quit their participation in the readability test, influencing the results. In this activity the assistance provided by Datamedica colleagues usually responsible for these activities was essential as well as Pharsolution's reviews and comments to the protocol and questionnaire.

The performance of the readability tests interviews was by far the most difficult activity in the readability test procedures. The trainee only had the chance to perform it once, but considered it a hard task. First, not all the people addressed were keen on taking the test, in spite of the trainee's assurance that they were not being assessed, but the document. This would slow down the recruitment and sometimes compromise the timeline of the entire process, especially in the medicinal products whose marketing authorization application required more volunteers for the readability test. Furthermore, the trainee had to deal with different volunteer's personalities that were difficult to handle and that could interfere with the test results. This could be related to the place where the tests were performed, due to the fact the volunteers recruited were at a pharmacy waiting to get their medicinal products or wanting to get home after purchase the medicinal product.

Finally, the trainee found the data compilation at the spreadsheet file as an interesting activity. The analysis indicated some "curious" facts, such as, the influence of the education degree on the evaluation of the readability, for example, people with higher educational degree would give lower scores to the different characteristics of the PIL being assessed. Moreover, these people would be the ones with faster answer times.

The trainee had already heard about readability tests before during her Biomedical Sciences Degree. It was quite useful for the trainee to be part of this regulatory affairs activity at Datamedica since she applied the theoretical knowledge to the reality, which is part of the accomplishment of learning outcome 3 for this internship defined in the introduction. Datamedica's structure and dynamics (section 1) provided the opportunity for the trainee to be part of this activity. In addition, the performance of readability tests was usually under a tight schedule, which required the trainee to, sometimes, put aside other activities and define priorities which contributed to improve the trainee's organizational skills.

The trainee also performed Medical Writing as part of the on the job training at Datamedica. Medical Writing shouldn't be considered as a completely separated activity from clinical trials monitoring due to the CRA's need to have a full inside knowledge about the clinical trial documents and be part of the process of development, organization and revision of these documents.

The literature reviews performed by the trainee to support CTs and other related activities, were one of the activities that required most effort to be accomplished. Firstly, since there were not many instructions about how the trainee should perform them and organize the resultant document, the trainee got worried, but soon realized that there was “free will” about the structure and content of the document, as long as the required content was organized and supported by reliable source documents. Also, in case of doubt her colleagues at Datamedica would always be available to provide assistance and support. These were some of the activities that better contributed to develop important team skills and good interpersonal relationships among the team colleagues and line managers (learning outcome 6 in the introduction). Secondly, some of the data/information required for the literature reviews was difficult to find even though the trainee was used to perform literature reviews and to search for information in articles and reliable websites. It was necessary to choose key terms that would lead to the desired information, that is, to find different strategies in the face of adversities as defined in learning outcome 9, in the introduction.

On the other hand, when it was necessary to find information about a particular disease (incidence, prevalence, treatments used, etc) or the CTs/studies developed in those diseases, the trainee had no problems with this activity.

Document revision and translation, two of the most common medical writing activities are part of the daily routine of a CRA (which constitutes more evidence about the connection between the medical writing department and clinical investigation). Right on the first month of the internship the first activity the trainee performed was the revision of the CRFs, informed consents information sheet and form and protocol. Being in contact with these documents for the first time and reviewing them was an interesting way of realizing which documents are essential in CTs, how they are usually structured and organized and what are the main points to pay attention to. This activity was how the trainee started acquiring in-depth knowledge about CT monitoring as mentioned in learning outcome 4 of the introduction. The easier documents to review in the trainee’s opinion are the informed consent’s information sheet and form. The most important characteristic of these documents is to see if they are clear and understandable to the patients and if they have all the information that CEIC requires to be provided to the patients.

However the most interesting medical writing activity to the trainee was CRF designing. The trainee found it challenging to design CRFs without the guidance of a protocol. There were, however, different background tasks in those CRFs. In the CRF designed for hepatitis some of the data that should be collected was provided to the trainee, but on the CRF about acute hemorrhoidal crisis the trainee had to perform a search about the disease and select the information that should be part of the CRF. In general, the difficult part of designing the CRF was putting the data in the CRF

in a way that would be easily answered and without formulating questions that required an open answer. The utilization of a previously made CRF template was extremely helpful in this task.

In general, the trainee feels that by being part of Medical Writing Activities, she had the chance to get to know another area of activity of the pharmaceutical world (which was also one of the goals of the trainee as becoming part of this world through the internship) that deals with documents, which the trainee feels that are indispensable in conducting clinical trials.

Focusing on monitoring activities, these were and still are the most attractive activity to the trainee and the one that defied the trainee abilities and skills more often. With each clinical trial/clinical study the trainee had different challenges to solve. Throughout the next paragraphs are mentioned several situations of adversities faced by the trainee and the resolution of these problems which demonstrates the achievement of learning outcome 9 and also learning outcome 4 since the trainee had to acquire/develop specific skills to solve these situations.

One transversal difficulty to all trials/studies is the struggle to contact the investigational teams of the trials/studies. The trial's investigational team members, will frequently only be reached after days of several contact attempts by different means (email, telephone, contacting the hospital unit where they work, etc). The telephonic contact is the preferable mean of contact, especially if the mobile phone number is available to the CRA. To get through this difficulty, it is easier if at each clinical trial site, a team member who is usually more available is selected, in order to get things done easily.

As most of the clinical trials monitored by the trainee were in the start-up phase, it was on this phase that most challenges and difficulties arose. The first difficulty found, related to the above concerns about investigational team availability, was the time it would take to collect the information and documents necessary to submit the clinical trial/study to the regulatory authorities. It is really difficult to define a very specific schedule for submission, since the CRA never knows when the principal investigator (which is the main contact at this phase) will be available to answer questions and give the necessary documents. One way to go around this situation is to schedule a day with the investigator and bring every necessary document prepared so that there are few pending issues (or none if possible, but unlikely).

The preparation of financial agreements for the clinical trials was one activity the trainee had much difficulty with. The trainee was astonished by the background work required for this activity. 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. At Astellas, adding to these already identified issues, there was the need to send the contracts for legal review by the international team which often led to subsequent changes of the trial contracts as well as developing bilingual contracts, that due to the technical contract language are difficult to do. This activity is an example of how learning outcome 7 was fulfilled since the trainee had to adapt to the Astellas' rules and regulations regarding contracts. This task needs to be performed before submission to the regulatory authorities, since the contracts are evaluated by CEIC and INFARMED. However, since the administration board of the sites only evaluates the contracts by the time the submission dossier is submitted to them, there may be some changes made by the sites that need to be notified to CEIC and INFARMED.

The Clinical Trials Submission to INFARMED, CEIC, and CNPD also brought a handful of challenges to the trainee.

When submitting to all these authorities there are some requirements that need to be taken into account in order to have the submission process validated and evaluated. Some of these specificities are ambiguous and if not answered correctly, may lead to non-authorization of the trial. The most ambiguous situation experienced by the trainee occurred with CNPD request for information after submitting their form. The CNPD requested information about transmitting information to countries outside EU, which lead to a request to the sponsor - APEL to prepare and sign a variety of new contracts with their vendors. Consequently delays occurred compromising the study timelines. In a CT performed in 36 countries only CNPD requested information about this issue which makes the trainee think that CNPD is a very competent entity, but also very strict. This is one of those issues that, as mentioned in section 1.5, may compromise the future development of CTs in Portugal.

In addition to CNPD, CEIC is also a very strict Committee, especially when assessing the material directly delivered to the study participants (e.g. informed consent). The main problem with CEIC is the time they take to evaluate the trial which may be extended if they request for clarifications. The trainee thinks that the clarification period is important but, she went through a situation where the clarifications asked were the correction of spelling errors and deleting commas, which even though it is important, it seems exaggerated due to the extension of the period to get their response.

In terms of submission to the clinical trial sites, it is important to be sure that all their requirements are fulfilled. In those sites that have a high number of requirements, it is more difficult to gather all the documentation. One setback with regard to the submission to the administration board is the fact that few clinical trial sites accept the submission dossier before CEIC's, INFARMED and

CNPD authorization, which contributes to delaying the time to get the trial to start. This was critical for the trainee, because of a really aggressive and competitive timeline of an Astellas' Urology CT with a seven months recruitment period. Considering CEIC's opinion was only available by the time recruitment was already on its third month, the crucial impact of these authorities approval times becomes evident.

Regarding the observational study monitored by the trainee, this study did not require approval from INFARMED and CEIC, only from the Local Ethics Committee and Administration Board. In some situations this means quicker approvals and easier beginnings (the trainee experienced a site that approved in one month and a half) but it may also mean long delays (on the other hand the trainee experienced a site that took nine months to approve a study).

During submissions and approval periods it is important to keep the investigational site staff teams interested in the trial. The importance of this update was evidenced with the Datamedica CT on the rheumatology area, whose regulatory authorities submission were delayed and some of the already selected sites quit the trial due to loss of interest in the trial.

At Astellas, while submitting the trial to the authorities, the trainee had the opportunity to attend an Investigator Meeting organized by APEL. This meeting was attended by two members of the investigational team of each site at the international level. This was a valuable experience for the trainee contributing to create stronger bonds with the investigational teams, by accompanying them during this meeting and making sure they had everything they needed while they are attending the meeting. These meetings contribute to establish a big contact network with professionals all over the world (learning outcome 5). These meetings were considered extremely important in the CTs context, as they allow to pass on and explain the trial to everyone involved, at the same time, and in the same manner. Furthermore, the participation of the international team members allows the exchange of ideas and the clarification of issues about the trial with everyone. During the same period of the investigator meeting, there was organized a monitoring meeting that lasted longer than the investigator meeting, and its main goal was to explain the CT procedures in detail to the CRAs.

The trainee considers monitoring visits to CT sites as the most important monitoring activities. The trainee performed three types of monitoring visits: pre-selection visits, initiation visit and periodic monitoring visits.

The pre-selection visits require some deep knowledge about the CT to answer all the questions that may rise, while introducing it to the investigational site and the principal investigator. While conducting this visit, it is important to contact the right person. Usually, the first contact is with the head of the hospital unit where the study shall be conducted and he then points the principal investigator of the trial. Sometimes, the first contact may be directly with the principal investigator.

This situation occurs when the principal investigator is already known, that is, it has already performed one of the company trials. In the pre-selection visits there are three different possible results: either the site accepts the trial and Datamedica or Astellas select it, or the site rejects the trial, or the site wants to conduct the trial but Astellas or Datamedica think the site does not have the suitable conditions and does not select it. While performing selection visits at Datamedica the trainee came across several rejections from the clinical sites due to inability to recruit patients with the required profile and at Astellas, there were situations where the sponsor did not consider the site had the suitable conditions. A major reason not to choose contacted sites is the understanding that the site staff does not have enough time to perform the study, and some of its members may not be interested in the trial, or there may be some issues with the administration board that makes it difficult to obtain CT approval.

Initiation visits were frequently performed by the trainee at Astellas and the main lesson taken from these visits is that the CRA must really understand the trial/study and be able to answer any question that may rise, because there are investigational site staff teams that are more difficult than others and ask about every detail of the trial. Usually the main issue with the initiation visits is that they take between two to four hours, depending on the trial, and the investigational team must be able to be present during this visit. It had happened more than once that the trainee had speeded up the initiation visit presentation because the team was getting restless and wanted to go back to work. Also, when the investigational team is big, it is difficult to schedule an initiation visit that can be attended by all team members. These visits usually are the first contact of the CRA with the entire team and it is how they learn how to conduct the trial correctly.

Periodic monitoring visits have different challenges. In these visits the trainee was in contact with the investigators and talked about how the trial was being conducted by the investigational team at the trial sites. This is very important since it shows that there is a commitment from both parts in performing the trial correctly and allows discussion of some problems that may have risen and the solutions to them. Again, these contacts should not occur only through periodic monitoring visits but frequently, by both telephonic contact and email. The CRA should always be available to meet the site staff team if requested. The most difficult activity in these visits is the source data verification that allows detecting any issue that may come up and ensuring the data are accurate, and the trials are being conducted properly and according to GCP. To do this, it is necessary to adapt to the different source documents of the different CT sites. When performing periodic monitoring visits, a comparative analysis is made between the information at the source documents of the patient and the information added to the CRF. To do this correctly and accurately it is important to know how the files of the subjects are organized to find the information that needs to be confirmed. The problem is that each CT site has its own organization and the CRA needs to

adapt to each unit organization. In addition, if a subject has had adverse events, it is necessary to verify if the AE has been reported correctly which is usually a laborious and time-consuming task. Usually the investigational team hasn't reported the AE and it is necessary to report what was found right away. Furthermore it may be detected incomplete or wrongly added data at the CRF and, since the investigational team is the only party authorized to make data changes, both at the CRF and source documents, the CRA usually calls the investigator during the visit to correct the information. This means that the monitoring visits will take longer, according to the investigational team availability. This reflects the importance of scheduling the periodic monitoring visit with the investigational team. One important feature that is worth mentioning is the fact that periodic monitoring visits can flow easier at the CT sites that have study site coordinators which can solve some problems detected by the monitor and correct CRFs, without having to wait for the investigators. In those cases, most of the issues that arise are dealt with the study site coordinator, which is, as the name indicates, in charge of coordinating the trials.

Despite what has already been discussed, the trainee would like to mention the importance of frequently updating the sponsor about the trial that is being performed. For example, at Astellas with the international trials, every month or even every week, a teleconference was scheduled with the sponsor and the other affiliates that were performing the trial in their countries. These teleconferences were one of the most important activities that the trainee had to perform and, usually, the study manager of the trial conducted them.

In general, while at both Datamedica and Astellas Farma the trainee had the chance to realize the importance of monitoring and of clinical trials in general, especially for the subjects taking part in clinical trials for whom it is needed to protect their rights and well-being which is part of the CRA's responsibilities since these subjects are helping in getting new innovative products to the market and to improve general healthcare. Knowing that she is being part of something this important made the trainee feel great.

It should be mentioned that, not only through the activities developed, Datamedica allowed the trainee to establish a professional contact network (learning outcome 5). Datamedica provided to the trainee the opportunity to attend the European Meeting organized by DIA (Drug Information Association). DIA - 24th Eurometing was considered one of the most positive and rewarding experiences to the trainee. This meeting was attended by thousands of professionals related to the pharmaceutical business, from different areas/departments and promoted networking between the attendees with speed networking, or networking lunches, etc, to exchange experiences and advices between them about careers, future etc. In addition this meeting also had booths/stands from different companies around the world, some of which the trainee had never heard of and that gave her a perspective of what was out there for career development. It was the first time she had

attended an event of this dimension and the experience was so valuable that the trainee intends to attend more of this meetings.

In the above paragraphs it were discussed the activities the trainee had the opportunity to perform during these ten months. In the following paragraphs a brief description about the activities that the trainee did not have the opportunity to do is being discussed.

The most important activity the trainee identifies as not being able to perform and that interferes with the learning outcome 2 about the clinical trial monitoring know how and responsibilities is the performance of CT close out visits. These are the only type of monitoring visits the trainee has never performed or even witnessed. This situation occurred because most of the trials the trainee was involved were at their set up phase or recruitment. Only the phase IV neurology CT was about to close but those visits were only performed after the trainee went to Astellas Farma Lda.

The trainee also would have liked to use the information systems created at Datamedica, especially COATI, since according to the description of the program and the opinion of the Datamedica's colleagues it is a very useful tool for clinical trial monitoring. The problem with this system is the fact that does not run in the trainee laptop. One other activity the trainee would have liked to do was, the possibility of performing pharmacovigilance activities at Datamedica. This because, since she was able to perform Regulatory Affairs Unit activities, which is linked to the Pharmacovigilance Unit, if she had been given the opportunity to perform some of these activities, she would have fulfilled learning outcome 10 (performing activities not related to CT monitoring) in a wider extent and would have given the trainee a wider knowledge about other pharmaceutical industry areas.

To complete this chapter, the trainee would just like to discuss how being part of Astellas and how the size of this company changed the way her work was performed. First, since the trainee was working in one of the CT sponsor's affiliate it would contact the sponsor more easily. Secondly, Astellas has many medical sales representatives that promote Astellas' products through the doctors and hospitals. These are the same institutions/investigators chosen for the clinical trials. This way, when the trainee was unable to reach a site team she could contact the sales representatives to help her. Finally the fact the medical and regulatory affairs department was bigger than the clinical investigation unit at Datamedica and the fact that at Astellas there was a Clinical Trial Assistant to help the trainee with files and folders, the work was better organized.

Finally, the trainee just wanted to acknowledge the change witnessed with the creation of Datamedica Angola. When the trainee was outsourced to Astellas, Datamedica had just created Datamedica Angola. The creation of this new affiliate was the way Datamedica found to deal with the economical crisis in Portugal. Angola is a receptive country in terms of pharmaceutical research and it is much more profitable to perform clinical trials in Angola, since healthcare is cheaper and

there are much more CT volunteers. For now, in Angola, Datamedica is performing training in the correct ethical principles and good clinical practices to develop the company further. It is very positive for both Datamedica and Angola to have this new company. From Angola's point of view it is good that Portugal is investing there to raise the economy and to Datamedica this is the first step taken to conquer the international market.

Lastly, with every activity the trainee had to perform she performed the best way she knew in a careful way and most of all successfully which fulfills the learning outcome 8.

#### **4 - Conclusion**

The ten months that have gone by were a unique experience to the trainee. They have marked the trainee's entrance in the professional world, which, as already discussed, was considered very positive. Datamedica welcomed the trainee and took care of her until she was ready to proceed by herself in a new company (Astellas) with a different dynamic and always backing her up - the trainee considered that being outsourced to Astellas was the best way to learn and grow in this business by herself. This was how the trainee was introduced to the professional world to develop her career and how she was brought closer to the pharmaceutical research world, specifically the clinical trials world.

By being part of two companies performing CTs and all its related activities the trainee got to know how this business worked from two perspectives (the company that sponsors the trials and the company to where services are outsourced) and what her responsibilities were and became a professional CRA. In addition as part of both Datamedica and Astellas all the theoretical knowledge gathered in the previous years of education finally gained practical application and the trainee realized the importance of this knowledge even though there were required some adaptations to reality.

The experience of these several months provided the trainee with skills and expertise essential to CT monitoring that could never be acquired through books or lectures, such as, how should the investigators be preferably contacted? In what manner can CRA offer assistance to investigators? How to strengthen relationships between CRAs and monitors? Working as a CRA during these last months has changed the trainee's personality – she became more self-confident to talk to the investigational teams of the clinical trial and argumentative, which makes a difference in the CRA's world. Also, these two companies allowed the trainee to create the first contacts of a professional network in the pharmaceutical research business, which is of great importance, especially in the Portuguese economical situation.

In the trainee's opinion there isn't a better professional activity to collaborate with a variety of professionals and to develop team skills and good interpersonal relationships. The trainee got to know and work with physicians, nurses, pharmacists, study managers, medical managers, medical advisors, medical information delegates, etc and realize their impact and role in clinical research.

With every activity the trainee faced during these 10 months she performed it the best way she knew. Sometimes she faced difficulties, e.g. with financial contracts and authorities' authorizations but with her commitment and support from colleagues, she was able to accomplish the proposed activities and solve adversities. The trainee considered being able to face adversities a major achievement.

Furthermore, she was able to perform activities outside CT monitoring that was the chosen area of the internship, such as medical writing activities and readability tests as already mentioned in the previous sections which evidences the completion of the last defined learning outcome.

By analyzing the defined learning outcomes, in a few words, the trainee considers that in general terms they were all achieved leading to the conclusion that Datamedica is a good place to take the on the job training / curricular internship. By having experienced the two stakeholders' environments (Astellas and Datamedica) and identified the benefits of being part of a big pharmaceutical company, the trainee considers that Datamedica was the suitable place to start out the CRA career, due to the fact big pharma companies such as Astellas do not focus exclusively on clinical trials and clinical research and do not have large teams of CRA/CRM. At Datamedica due to high focus on clinical research the trainee had more colleagues performing clinical trials monitoring to learn from, which was essential to the trainee, especially when she was outsourced to Astellas. Besides experience, first perspective on the clinical research-working environment, company dynamics and staff responsibility, Datamedica provides opportunities to expand the trainee curriculum in addition to good companionship, teamwork values and to personal growth.



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