**Universidade de Aveiro** Secção Autónoma de Ciências de Saúde
**Ano 2014/ 2015**

**Margarida Isabel de Sousa Vicente**

# RELATÓRIO DE ESTÁGIO CURRICULAR NUMA *CRO FULL SERVICE*

# REPORT OF A CURRICULAR INTERNSHIP AT A FULL SERVICE CRO

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção de grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica de Maria João Santos, *Scientific and Quality Assurance Manager* da DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., e do Professor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Curricular internship report presented to the University of Aveiro to fulfil the necessary requirements for the Master's Degree in Pharmaceutical Medicine, held under the scientific guidance of Maria João Santos, Scientific and Quality Assurance Manager at DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., and Professor Bruno Gago, Invited Assistant Professor at Health Sciences Department of the University of Aveiro.

**o júri**

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**palavras-chave**

*CRO*, Estágio, Estudos Clínicos, Estudos Farmacoeconómicos, Investigação Clínica, *Medical Writing*, Monitorização.

**resumo**

O presente relatório descreve as atividades desenvolvidas e a experiência adquirida durante o estágio curricular realizado na DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., no âmbito do Mestrado em Biomedicina Farmacêutica.

O estágio, que decorreu de Setembro de 2014 a Abril de 2015, permitiu a realização de diversas atividades relacionadas com Investigação Clínica, das quais se destacam: preparação de submissões de estudos clínicos às Autoridades Competentes; monitorização; *medical writing* e *data management*.

Todo o trabalho desenvolvido durante este estágio foi fundamental para a aquisição de novas competências e desenvolvimento de antigas, tais como comunicação, concentração, sentido de responsabilidade, organização e resposta em situações de *stress*, que contribuíram para uma melhor preparação a nível profissional, pessoal e social face à Investigação Clínica e seus principais *stakeholders*. Adicionalmente, o estágio permitiu contactar com as atividades do quotidiano de uma *Clinical Research Organisation (CRO) Full Service* e colocar em prática os conhecimentos adquiridos durante a formação na Universidade.

**keywords**

CRO, Internship, Clinical Studies, Pharmacoeconomical Studies, Clinical Research, Medical Writing, Studies Monitoring.

**abstract**

The present report outlines the activities developed and the acquired experience during the curricular internship at DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., under the scope of the Pharmaceutical Biomedicine Master Course.

The internship, which took place between September 2014 and April 2015, allowed the performance of several activities related to Clinical Research, namely preparation of clinical studies submissions to Competent Authorities; monitoring activities; medical writing and data management.

The work developed during this internship was essential both to acquire an important basis regarding new professional, personal and social skills and to develop old ones face to Clinical Research and its most relevant stakeholders, such as communication, concentration, sense of responsibility, organisation and correct response in stressful situations. The internship also allowed me to contact with the daily life activities of a Full Service Clinical Research Organisation (CRO) and put into practice the knowledge acquired at the University.

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## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AoR | Acknowledgment of Receipt |
| APIFARMA | *Associação Portuguesa da Indústria Farmacêutica* (Portuguese Association of Pharmaceutical Industry) |
| BIA | Budget Impact Analysis |
| CA | Competent Authorities |
| CDMS | Clinical Data Management System |
| CEA | Cost-Effectiveness Analysis |
| CEC | Competent Ethics Committee |
| CEIC | *Comissão de Ética para a Investigação Clínica* (Ethic Committee for Clinical Investigation) |
| CNPD | *Comissão Nacional de Proteção de Dados* (Portuguese Committee for Data Protection) |
| COV | Close-Out Visit |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Clinical Research Organisation |
| CV | *Curriculum Vitae* |
| DM | Data Management |
| EBM | Evidence Based Medicine |
| EC | European Commission |
| EMA | European Medicines Agency |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| GCP | Good Clinical Practices |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IF | Investigator File |
| IIS | Investigator Initiated Studies |
| IMP | Investigational Medicinal Product |
| INFARMED | *Autoridade Nacional do Medicamento e Produtos de Saúde* (National Authority of Medicines and Health Products) |
| ISF | Investigator Study File |
| ISO | International Organisation for Standardization |
| MV | Monitoring Visit |

| | |
|---|---|
| MW | Medical Writing |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PF | Pharmacy File |
| QA | Quality Assurance |
| QALY | Quality-Adjusted Life Year |
| QMS | Quality Management System |
| RCT | Randomised Controlled Trial |
| RNEC | *Registo Nacional de Estudos Clínicos* (National Registry of Clinical Studies) |
| ROI | Return On Investment |
| SAE | Serious Adverse Event |
| SC | Study Coordinator |
| SDV | Source Data Verification |
| SIV | Site Initiation Visit |
| SOP | Standard Operating Procedure |
| TMF | Trial Master File |
| USF | *Unidade de Saúde Familiar* (Family Health Unit) |
| WMA | World Medical Association |

# 1. INTRODUCTION

The present work consists on a curricular internship report developed under the scope of the Pharmaceutical Medicine Master Course at the University of Aveiro. Due to my desire to start the internship earlier, I started to work as a trainee at DATAMEDICA on June 2014. However, the curricular internship only took place between September 2014 and April 2015 at DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., and, therefore, this report will only mention the activities performed during that period.

During the internship period I held a Clinical Research Associate (CRA) Trainee position. However, the internship also intended to provide me with a much broader perspective of the working environment and to introduce me to all the Company's projects. Thus, I executed several activities beyond CRA position, such as medical writing, pharmacoeconomic studies, data management and quality assurance (QA).

This report describes my experience as a trainee at DATAMEDICA and addresses the internship objectives, discussing the challenges, skills and knowledge acquired.

The selection of DATAMEDICA as the host company of my internship was advised by my Master's Professors. Besides their opinion, it was also my intention to conduct the internship at a CRO because I wanted to obtain knowledge and experience in other fields than clinical studies monitoring. Due to my willingness to learn and work, it was given to me the opportunity to start performing activities before the period of the curricular internship.

This report presents the activities developed during the internship at the Host Institution, as well as all the learning outcomes and skills acquired during this training period. In general terms, this report will address the structure and operating procedures of the Host Company and the current state of the art in Clinical Research, namely applied legislation, regulatory authorities and, finally, a little glimpse about Portuguese and European Clinical Trials framework. A brief introduction to each theme and training area mentioned above will be given, the most relevant activities performed will be described, and the way these activities were performed will be explained. A discussion of the relevant aspects of this training period, detailing the problems and challenges faced and all the positive aspects identified will help to understand how the proposed learning objectives were achieved. Also, the conclusions taken from this period and the impact of these seven-months on personal and professional growth will be presented.

## 1.1 Internship Objectives

The main objective of this internship was to attain new knowledge and competences in Clinical Research, since the conception, submission and implementation of clinical studies, to the critical interpretation of data and publication of studies' results. The development and achievement of the main objective was initially proposed to be attempted by the following tasks:

- Collect practical knowledge about the operating procedures of Clinical Research and related responsibilities;
- Apply and consolidate the theoretical knowledge acquired at the Pharmaceutical Medicine Master Course and at Biomedical Sciences Degree;
- Establish professional contacts through the collaboration with other Clinical Research professionals;
- Develop important teamwork skills and good relationships with DATAMEDICA's colleagues and other professionals of the area;
- Know the principal methodologies used in the conception, development and implementation of clinical studies;
- Acquire competences for protocols' conception, study design and implement methodologies to avoid bias during study conduction.

More specifically, this internship aimed to obtain knowledge and practice on the following tasks:

- Perform all the tasks according with the Good Clinical Practices (GCP) and with the Host Company's procedures;
- Acquaint with the Host Company dynamics;
- Support the Host Company in all its projects;
- Perform all the tasks in a careful and precise way and within the predefined deadlines;
- Participate in training activities;
- Submission of clinical studies to competent authorities;
- Implementation of clinical studies at the study's sites;
- Perform co-monitoring visits at the study's sites;
- Acquire important competences in quality assurance, medical writing, data management and statistics related to Clinical Research.

## 1.2 Host Company

CROs are external and independent entities that supply consultancy services to all players of Clinical Research area. DATAMEDICA, Serviços e Consultoria em Bioestatística, Lda., is one of the most relevant CRO in national territory, supporting Pharmaceutical Industry, Health Care Professionals, International CROs and other entities dedicated to Clinical Research area.

At the date of its creation, in 1996, DATAMEDICA just provided biostatistical consultancy services, however, in response to the Market's needs, the consultancy services were extended to a much broader number of services. Nowadays, DATAMEDICA supports Clinical and Epidemiologic Investigation, namely Protocol development, Case Report Form (CRF) design, Study Logistics definition and implementation, Study Submission to Competent Authorities (CA), Study Monitoring and Back-Office support, Data Management (DM) and Statistical Analysis. It also offers Medical Writing (MW) services and support of abstracts/articles' submission process, Meta-Analysis, Expert Panels, Advisory Boards and Consensus services (preparation, development, implementation and support) and Pharmacoeconomic studies. Due to the quality of its services, flexibility and adaptation capacities of its multidisciplinary team, DATAMEDICA has achieved a strong reputation among national and international Clinical Research stakeholders.

During this internship, DATAMEDICA provided services to more than 25 Pharmaceutical Companies, Health Professionals Societies and CROs from Europe and United States of America.

Recently, DATAMEDICA incorporated the INTERWAY Group, created in 2003 and which focus is on the development and implementation of several projects and seeking of new opportunities in emerging markets, mainly in Sub-Saharan Africa. Guided by a policy of continuous expansion and development, the Group has already economic activities and operations in Angola, Mozambique, Sao Tome and Principe, Brazil and Portugal, with several areas of activity: Workspace Optimisation, Logistics, Operation and Management of Shopping Centres, Interior Design and Architecture, Technology, Health, Luxury Retail and Corporate and Business Consulting.

DATAMEDICA has an Administration Board, a Financial and Administrative Department, an Executive Management and Commercial Department, and a Scientific Department. The Scientific Department is the main core of DATAMEDICA's technical and scientific work and encompasses most of the activities related to clinical studies. The Research & Development Unit is mainly responsible by clinical studies design, bibliographic research to support clinical studies and development of clinical studies' protocol, both as CRF design and informed consent preparation. Clinical Operations Unit is more focused on submission and monitoring of clinical studies. DM & Statistical Unit performs all the tasks related to data management, such as database design, query resolution and database cleaning, also participating in CRF design. Regarding statistics, its main focus concerns statistical analysis data of clinical studies, critical interpretation of the data, and statistical reports development. DATAMEDICA is also involved in other activities, suchlike sample size calculation and respective rational, statistical analysis plan conception, interim analysis

performance, and protocol support regarding statistical section. Medical Writing Unit is in charge of abstracts, posters and articles, both development and submission, oral communications support, advisory boards/ expert panels transcription and report. At last, Regulatory Affairs & Pharmacovigilance Unit performs mainly outsourcing activities on the scope of pharmacovigilance. The organisational chart of DATAMEDICA is displayed at Figure 1.

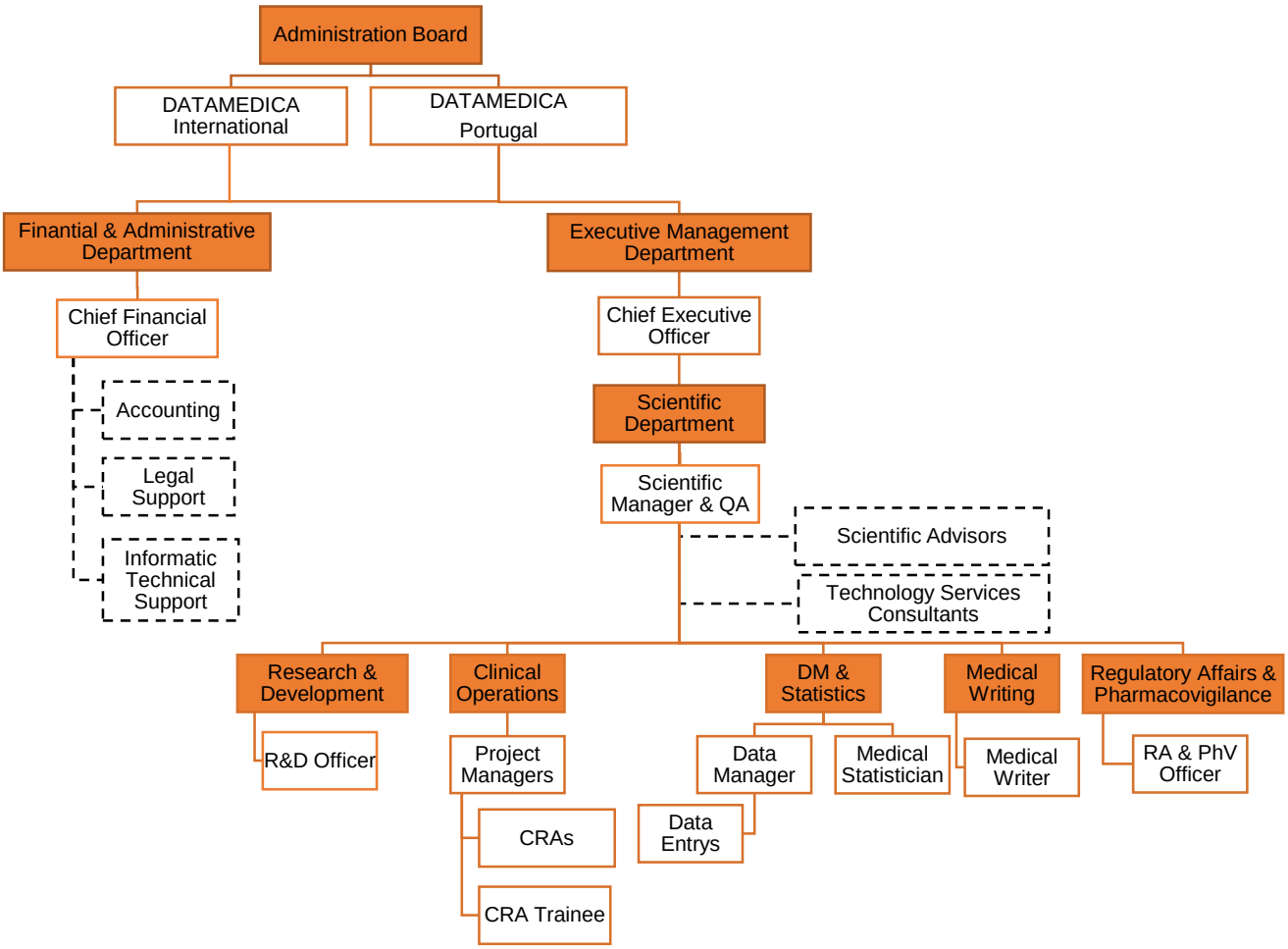


**Figure 1**. DATAMEDICA's organisational chart (DATAMEDICA's Internal Procedure)

It is important to notice that some of these departments are formed by just one person due to the size of the company. So, this is a small company with 10 employees, which facilitates social interactions between colleagues and the crossing of information in the different areas of expertise and contributes to the maintenance of collaborators' continuous learning process. Although each worker has his own area of expertise, all the projects developed and in progress are discussed by

the team and a multi-task ability to follow the projects and to perform the tasks required is mandatory.

A biweekly meeting is held at DATAMEDICA with all the operational collaborators. The main purpose of this meeting is to discuss DATAMEDICA's projects, mainly concerning a brief status of each project and an analysis of critical points or raised problems or issues. These meetings were implemented by Quality Assurance Department and helped sharing the work of each collaborator to the team and discuss different opinions, experiences and resolutions, while receiving feedback

## 2. STATE OF THE ART – CLINICAL RESEARCH

As DATAMEDICA performs their services in the Clinical Research area, it is important to give to the readers an introduction to this field. Therefore, this chapter will present a global overview of this area introducing its main features. Moreover, the stakeholders and their roles in Clinical Research will be summarized as well as the regulatory framework. Competent Authorities (CA), responsible for the interventional studies and health technologies' evaluation will be also introduced. At last, the current state of art of Clinical Research in Portugal compared to Europe will be presented.

Clinical Research is an enormous field of investigation and its development began because human civilisations always had a special interest in the health of Man and other animals, which led to the discovery of a large number of therapeutic agents in nature. (1). Clinical Research has been growing up and, due to the involvement of a large number of pharmaceutical companies and many academic institutions, there was a major progress in the regulation field, in the knowledge of the diseases' processes and in the creation of health technologies to prevent, control or eliminate it.

Any systematic study conducted in humans with one of the following objectives can be defined as Clinical Research: to discover or verify the distribution or effect of health factors, conditions or health outcomes and/or to understand the causes, progress and consequences of diseases; improve prevention, diagnostic and therapeutic interventions (methods, procedures and treatments) by studying its performance, safety, efficacy and effectiveness, efficiency, accessibility and quality (2, 3).

Clinical Research gives an important assistance to health care by finding evidences that support and allow good clinical decisions. Evidence Based Medicine (EBM) is a medicine practice in which decision-making is optimized by the use of evidence from well designed and conducted Clinical Research studies. Evidence may be obtained with different strategies: meta-analysis, systematic reviews, randomised Controlled Trials (RCT), non-interventional studies (such as case-control or cohort studies), non-analytical studies (such as case reports or case series) and experts' opinion. However, these studies have different levels of evidence strength and, therefore, depending on the question, the most evident and strong strategy will vary. Due to their design and methodologies, it is understandable that meta-analysis and systematic reviews, followed by RCT, have a higher level of evidence and represent an important research activity with the potential to improve the quality of health care and control costs through an accurate comparison of alternative treatments. Yet, all the studies should be assessed regarding their validity, results and relevance (4-6).

During the internship, DATAMEDICA provided services in the scope of RCT, interventional studies with medical devices, non-interventional studies and experts' opinion panels, with great validity in Clinical Research and very important to EBM. This report will try to cover all the relevant points of

these studies, which represents a great challenge due to all the factors involved in health sector and due to all the specifications of the transversal areas tangled with Clinical Research.

Clinical Research is accomplished within a highly regulated environment because it involves human participants, human material and/or human data. The participation of human subjects raises several ethical issues once their safety and rights must always be protected and guaranteed. Based on the Nuremberg Code, World Medical Association (WMA) compiled the Declaration of Helsinki, which is a set of ethical principles for Clinical Research involving human participants that includes research on identifiable human material and data. Even though Declaration of Helsinki is not a legally binding document under the international law, its authority is supported by its influence on the development of national or regional legislation and regulations (2).

Additionally, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) creates documents that make recommendations regarding scientific and technical aspects of drugs' development and registration. ICH Guidelines preparation involves the regulatory authorities and the pharmaceutical industries of several countries all over the World, with the final objective of achieving a greater harmonisation between all of them, ensuring that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner (7). It is important to refer ICH Guideline E6 "*Guideline for Good Clinical Practice*" as it is an international reference that gives support on the designing, conducting, recording, and reporting studies that involve human participants regarding mainly ethic and scientific quality considerations (8). Training on this guideline is mandatory for all the involved individuals and entities in Clinical Research area, mainly to those involved in interventional clinical studies, such as Clinical Trials.

In Europe, European Commission (EC) creates legislation applied to the pharmaceutical sector, which is compiled at Eudralex. European Medicines Agency (EMA), a decentralised agency of the European Union (EU), is responsible for the scientific evaluation and continuous supervision of medicines for human or veterinary use in the EU. Mainly, EMA scientifically evaluates applications for marketing authorisations in EU through centralized procedure, providing an opinion on the submission application helping the EC's final decision, and coordinates the EU's pharmacovigilance system (9).

The most important European directives and regulations regarding Clinical Research are:

- Directive 2001/83/EC and Regulation (EC) No 726/2004, which define the requirements and procedures for the marketing authorisation of human use medicines and give guidelines on the continuous supervision of products after marketing introduction;
- Directive 2001/20/EC and Regulation (EU) No 536/2014, which define the requirements for conducting Clinical Trials in the EU;

- Directive 2005/28/EC, which defines the principles of GCP for Clinical Trials on human participants involving investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products;
- Directive 2007/47/EC, which amend Directive 90/385/EEC on the approximation of the laws regarding active implantable medical devices, Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market.

Other European directives and regulations are important but are specific to other scopes, such as medical devices development, medication manufacturing, distribution and labelling, pharmacovigilance, orphan medicinal products, between others.

In Portugal, the monitoring, regulation and supervision of medicines, medical devices, cosmetics and body care products is a responsibility of INFARMED (*Autoridade Nacional do Medicamento e Produtos de Saúde*) and these are done according to the highest quality and safety standards. This institution also assures the access of health professionals and citizens to effective and safe medicines, medical devices, cosmetics and body care products with the required quality (10).

Besides INFARMED, clinical studies must be assessed by CEIC (*Comissão de Ética para a Investigação Clínica*), which is the national ethics committee for Clinical Research. CEIC is responsible to assure the rights, safety and well-being of human participants (11), and by CNPD (*Comissão Nacional de Proteção de Dados*), which is a national public institution that controls and verify sensible personal data handling, assuring the compliance with human rights and legal regulations (12).

Most relevant Portuguese legislations regarding Clinical Research are:

- Law No 21/2014, which is a transposition of Directive 2001/20/EC and that have recently revoked Law No 46/2004;
- Law No 102/2007, which is a transposition of Directive 2005/28/EC;
- Law No 67/98, which establishes the principles and requirements for personal data handling and free movement of personal information and it is a transposition of Directive 95/46/EC;
- Law No 145/2009, which establishes the rules to medical devices investigation, manufacture, commercialization, vigilance and publicity and it is a transposition of Directive 2007/47/CE.

Besides this regulatory framework, INFARMED, CEIC and CNPD have published several guidance documents establishing the requirements regarding specific considerations such as the request for clinical studies' authorisation, notification of substantial amendments, data handling, and studies results' publication.

According to European directive 2001/20/EC, Clinical Trials are defined 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"* and this definition has been transposed into National Law No 21/2014 (3, 13).

Additionally, National Law No 21/2014 distinguishes Clinical Trials from other clinical studies, which are any systematic studies, conducted on humans or through individual health information, intended to discover or verify the distribution or effect of health factors, health conditions or health outcomes; health course and disease evolution; and to understand and evaluate the performance and/ or safety of clinical technologies or health care, through biological, behavioural, social or organizational aspects. The following are examples of clinical studies: a study that evaluates an intervention which is different from clinical practice; a study involving medical devices; a study of alimentary regimens or a study involving cosmetics and body care products (3). Clinical studies also include non-interventional clinical studies, in which medicines or medical devices are used according with their marketing authorisation or conformity assessments' procedures, respectively, and the participants' inclusion in a particular therapeutic strategy just depends on clinical practice and is not decided in advance by a Clinical Study's protocol. Also, during non-interventional clinical studies, the prescription of a drug or the utilisation of a medical device is clearly independent from the decision to include the patient in the study, no monitoring or additional diagnostic procedures are applied and epidemiological methods are used for the analysis of the collected data (3, 14).

Pharmaceutical industries are the main boosters of Clinical Trials aiming to obtain data on the safety and efficacy of medicinal products that are being developed. Approximately 40% of the Clinical Trials in the EU are being conducted by academics, hospital or research networkers (often referred to as 'non-commercial Sponsors'), usually, to improve and compare treatments with authorised medicines (15). DATAMEDICA provides services to clinical studies sponsored by pharmaceutical industry and to Investigator Initiated Studies (IIS), which are studies initiated by academic or non-academic institutions or by health professionals, without commercial interests, although often supported by pharmaceutical industries. In IIS, the investigator assumes responsibility regarding study's initiation, management and/ or financing, while conducting the study (8). IIS principal aim is to improve the scientific knowledge and patient care and may be focused on potential diagnostic and therapeutic products not attractive or without commercial interest. This allows to provide the necessary evidence to the conception of treatment guidelines and to assure the proper use of the resources. Typical examples of IIS are proof-of-concept studies, rare diseases (orphan medicines), diagnostic or therapeutic interventions comparison, surgical therapies or novel indications for already marketing products (16). As referred before, IIS are supported by pharmaceutical companies, which benefit with the collection of additional safety

and efficacy data and useful information to support new indications or to be included on the marketing authorisation dossier.

To enhance studies' efficiency, while saving resources, Sponsors of clinical studies rely on Contract Research Organizations (CROs) like DATAMEDICA. According to ICH E6, a CRO is defined as "*a person or an organization (commercial, academic, or other) contracted by the Sponsor to perform one or more of a Sponsor's trial-related duties and functions*", which must be specified in writing. However, the Sponsor have the ultimate responsibility for the quality and integrity of study's data (8).

CROs' main objective is to improve the efficiency and financial performance of the Client, while providing more benefits to authorities, health professionals and citizens. These organisations provide services with the intent of improving and accelerating clinical studies, resulting in a superior return on investment (ROI) for the new product, reducing cycle time, while increasing the quality of study's data (17) and maintaining the independency from commercial or other type of interests.

Nowadays, there are CROs that provide a full service support, others that are specialised in a distinct area of Clinical Research, and Site Management Organisations (SMOs) that support the centres in clinical studies-related issues (17).

Regarding Clinical Research state of the art in Portugal, the number of Clinical Trials' application submissions to INFARMED is slowly decreasing. Between 2006 and 2014, the number of submissions decreased from 160 to 127, reaching the lowest number of Clinical Trials' submission in 2011, with only 88 submissions. A large part of the submitted studies are confirmatory or post-market multicentre Clinical Trials and, approximately 20% of the Clinical Trials are phase I or II.

In 2013, the majority of the Clinical Trials conducted in Portuguese sites were focused on oncology and immunomodulators therapeutic areas (42%), followed by anti-infectives (13%) and cardiovascular system (11%) (18). In this period, approximately 93% of the submissions made in each year came from pharmaceutical industries, compared to IIS's submissions which are much less in Portugal. Thus, in 2013, pharmaceutical industry submitted 98 Clinical Trials to evaluation versus 16 Clinical Trials submitted to evaluation by academic Sponsors. When we assess the number of conducted Clinical Trials at 2013, Portugal had 159 active Clinical Trials, a very small number compared to Spain which had 858 Clinical Trials and to United Kingdom with 832 Clinical Trials (18, 19).

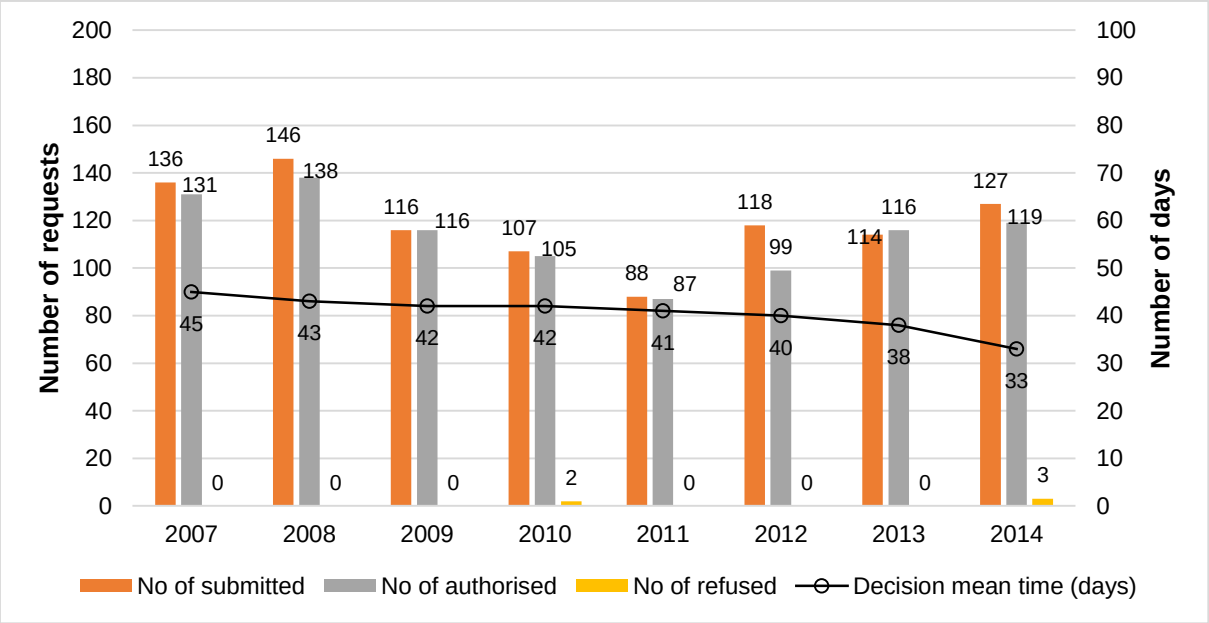


**Figure 2**. Clinical Trials' authorisation requests to INFARMED (19)

Regarding Portugal approvals' times, clinical studies application approvals may take 60 days, theoretically. However, the real period can exceed 70 days, in average, when taking into account the approval time taken by the Administration Board of the sites (18). The inefficiency of the assessment process by all the involved parties such as CNPD and Site's Administration Boards is one of the critical aspects that have diminished Portugal competitiveness versus other European countries.

In summary, Clinical Research is a complex network with several players, all of them with specific responsibilities and functions. An efficient communication and interaction between all these players is essential to enhance the number of clinical studies in Portugal, bringing the country "back to the competition". The increase of Clinical Research conducted in Portugal would bring a lot of benefits to our country and its citizens namely an earlier access to innovative and better treatments and also, concerning social and financial benefits, Clinical Trials would increase employment opportunities and enhance savings on the health spending.


**Figure 3.** Stakeholders of Clinical Research

More information can be given to introduce Clinical Research and all its specific branches as studies' conception, Clinical Trials' submission and monitoring, medical writing, pharmacoeconomic studies or other. However, to facilitate the comprehension of the reader, this specific information regarding the framework of each Clinical Research branches will be given separately in the next sections.

## 3. INTERNSHIP ACTIVITIES

The main focus of this chapter is to describe the activities developed during the 7-months internship.

The internship was much diversified and provided me the opportunity to perform a very large range of activities since the initial conception and development of the clinical studies to study results' analysis, reports development, along with transversal activities such as medical writing, quality management system (QMS) revision, and pharmacovigilance. Therefore, this chapter is divided in 8 sections, each related to the activities developed during the internship: Conception & Development of Clinical Studies; Studies' Submission; Monitoring Activities; Data Management; Pharmacoeconomic Studies; Advisory Boards and Expert Panels; Medical Writing and Quality Management System related activities. In each section, the procedures usually followed to achieve the task and its specific aims will be described. A brief introduction to the scope and the relevance will be given to help the understanding of these themes.

Before internship activities description, it is important to mention that prior to receiving any information related to DATAMEDICA's Projects or Clients, every collaborator must sign a Confidentiality Agreement concerning all sensitive and confidential information that the collaborator can manage while working at DATAMEDICA. In this report, it would not be mentioned or shared Clients' names, study's protocol or health products information, nor any personal data of study participants. However, information of public access, such as Clinical Trials names or general information about them, may be shared.

## 3.1 Conception & Development of Clinical Studies

The conception of a Clinical Study (Interventional or Non-Interventional) begins with the formulation of a relevant hypothesis. Usually, the Client wants to support a new marketing authorisation, a new indication or a new formulation for a medicine already in the market or wants to understand a specific feature on the real population. After the objective's definition, the experience of DATAMEDICA's collaborators is essential to help the Client on the definition of study design and methodology regarding its main goal: should we perform a Clinical Trial or a non-interventional one? Should a Clinical Trial have a parallel design or should it be cross-over? Should it be double-blind? Randomised?

There are a large set of questions that must be answered when conceptualizing the study, which affects the study's results and quality, as well as the study's budget, without neglecting the rights and safety of human participants. The definition of an adequate design is crucial, once that can negatively influence the quality of the data and diminish study's results validity. Therefore, the conceptualisation of a study should involve both the Client, an expert in studies' designs and methodology, a biostatistician and a health professional specialised in the area. It is important to understand the Client's goals and the study's specific objectives.

Study's endpoints can be divided in two: efficacy and safety endpoints. Primary efficacy endpoints must allow to assess and give clinically relevant and undeniable evidence directly related to the study's primary objective (20). Generally, there is just one primary efficacy endpoint for each study. However, in specific cases, a multiple primary endpoint could be defined, which will imply a different statistical methodology, than the commonly used. To support the selection of the endpoint, EMA published several directives focused on specific diseases and research that give recommendations for endpoint's definition as well as other important considerations that should be taken into account (21).

During Clinical Trial's conception, I performed a bibliographic revision about the theme in question, followed by a self-training that included: prevalence and incidence of the condition in Portugal, Europe and worldwide, signs and symptoms, causes, methods of diagnostic, current treatments and follow-up procedures. A profound knowledge on the study thematic is helpful to assess the viability of a specific design. In this case, a cross-over design was not viable because the progression of the disease is variable and therefore it was not possible to assure that the patients will exhibit a similar severity of the disease during study conduction.

Regarding the same project, it was decided that both health professionals and patients should not know the treatment that each patient received (double-blinding) because clinical response to the treatment was subjective and dependent on patient's opinion. In this specific study, a logistic problem was raised with this decision because the Investigational Medicinal Product (IMP) had a different formulation than the active comparator and, for that reason, DATAMEDICA recommended the double-dummy technique, which is used when the two treatments cannot be made identical.

Study's evaluation procedures and their schedule are dependent on the mechanism of action of the investigational product and on the study objectives. During evaluation procedures, it is really important to discuss with a health professional the possible exams, procedures and understand the clinical practice in Portuguese centres. However, besides the support of the health professional, an exhaustive bibliographic revision must be performed. National health system publishes guidelines focusing a specific disease regarding both diagnostic and treatment methods.

Another relevant point that must be addressed during the study's conception phase is the target population and the sample size. In the studies that DATAMEDICA have managed, the definition of the target population was clear. However, the selection of eligibility criteria requires an extensive literature revision in order to comprehend the product mechanism of action, influencing factors and the disease. All the possible factors that could change the study's results must be controlled and minimized to maintain sufficient homogeneity and, therefore, to allow a precise estimation of treatment effects (20).

Regarding sample size, how many participants should be included on the study to achieve its objectives? Sample size should be large enough to give reliable answers to the study endpoints and to allow to reject or accept the initial study's hypothesis (20). Sample size determination requires the previous definition of the primary efficacy endpoint, the null and alternative hypothesis and it depends on the size of the expected effect on the primary efficacy endpoint and its variability, the probability of wrongly reject the null hypothesis (the type I error), and the probability of incorrectly fail to reject the null hypothesis (the type II error). ICH guidelines recommend the use of type I error set at 5% or less and the use of a type II error set at 10% to 20% (20). During the internship, I had the opportunity to support the medical statistician during sample size calculation, once that it was necessary to define the prevalence of the disease and, for that, I had to perform a bibliographic research to find the update and reliable data.

When the study's objectives and methodology are defined, the development of study documents can begin. The most important document is the Study's Protocol, which describes the study's objectives, design, target population, methodology and statistical considerations (13). In the Protocol, it is also given an introduction to the theme in question and the study rationale is detailed, as well as ethics considerations and other administrative relevant points. ICH E6 "Good Clinical Practice" defines the main topics that must be addressed on the Clinical Study's Protocol (8).

The Study's Protocol will support the appraisal of the Competent Authorities and will support the chores and duties of the Study's Team since participants' recruitment until close-out. Therefore, a good Protocol facilitates external review of the study, its correct conduction and final reporting (22).

During the internship, I had the opportunity to create several study documents such as Study's Protocol, Informed Consent Form (ICF), Patient Information Sheet (PIS) and CRFs. I also had the opportunity to support other documentation development regarding non-interventional studies.

This experience enabled me to acquire more knowledge about studies' methodology, such as randomization and blinding techniques, along with more specific understanding of biostatistical considerations and also the particular structures and functions of study's documentation.

The implementation of a Clinical Trial requires an enormous logistics that must assure that all the possible risks or failure are identified prior to the implementation and that all the possible actions to minimize the possibility of risks' occurrence are taken. Besides these, there are other tasks that must be conducted before the submission of the trial to all the required entities, such as the definition of the medicine circuit, the development of medicine batches according to Annex 13 of the 4$^{th}$ volume of EU Guidelines to Good Manufacturing Practice, Insurance Certificate contract, and the purchase of specific items to be given to the sites (e.g. scales, blood pressure monitors, stadiometers and pregnancy tests).

## 3.2 Studies' Registration and Submission

Studies' registration is important to increase transparency, avoid unnecessary duplication of Clinical Research, facilitating the identification of ongoing, completed or terminated studies and allow us the overview of all Clinical Trials and also the performance of statistical analysis regarding general picture (22). Regarding the submission of the clinical studies to Ethics Committees or to Competent Authorities, such as INFARMED, the evaluation of the benefits and risks involved in the study must be addressed mainly regarding the Study's Protocol, the study team and the centres proposed, the Investigator Brochure, the ICF and the Insurance Certificate (13).

During the internship, DATAMEDICA participated on the registration and submission to ethics committees, INFARMED and Administration Boards of several clinical studies, such as Clinical Trials and non-interventional studies. The graphic 2 shows the number of registrations and submissions performed by me during the internship and the table 1 summarizes the activities that I performed in each one of them.

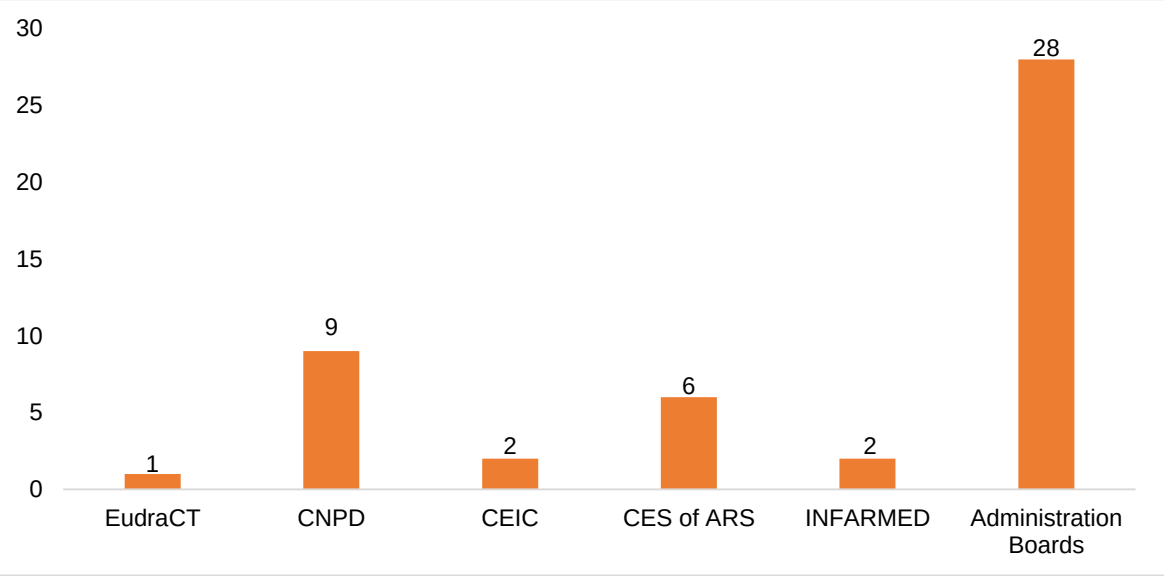


**Figure 4.** Number of Registrations and Submissions of Clinical Studies performed during my internship

**Table 1.** Specific tasks that I have performed during my internship, regarding registration and submission of Clinical Studies

| Activity | Specific tasks performed/ assisted |
|---|---|
| EudraCT Registration | • Filing of online form to obtain the EudraCT number for CTs.<br>• Completion, revision and modification of XML files support. |
| CNPD Submission | • Filing of online forms.<br>• Send of study documents (study synopsis, CRF and informed consent) to CNPD.<br>• Reply to requests for additional information regarding the relevance to collect an ethic variable.<br>• Follow-up of the processes' evaluation. |
| INFARMED Submission | • Preparation of cover letters.<br>• Documents archive in a folder scheme according to INFARMED directives.<br>• In person delivery of CTs submission. |
| CEIC Submission | • Preparation of cover letters.<br>• Documents archive in a folder scheme according to CEIC directives.<br>• In person delivery of CTs submission. |
| Study Sites Submission | • Sites' contact to request local requirements and applicable templates before studies' initiation.<br>• Preparation of cover letters.<br>• Discussion and development of financial agreements.<br>• Documents archive in a folder scheme according to Site's specific directives.<br>• Filing of site specific forms and adaption of Site's templates.<br>• Sending additional documentation and answering the questions raised during process evaluation.<br>• Follow-up of the processes' evaluation. |

### 3.2.1 Studies' Registration

In Europe, CT registration is an actual requirement based on ethical and scientific reasons and must be carried out before the inclusion of the first subject. EudraCT is the European Clinical Trials Database, an open public database, which collects information of all Clinical Trials involving investigational medicinal products occurring in, at least, one site in the EU (23).

To apply for a EudraCT number at the EudraCT website, information about the requestor's organisation and the Clinical Trial in question is required:

- Requestor's organisation name, town/ city and country;
- Sponsor's Protocol code number;
- Contact person's name and e-mail to whom the EudraCT number will be sent;
- Whether the Clinical Trial is contained in a Paediatric Investigation Plan (PIP) or whether it will be conducted in a third country (outside of the EU/EEA);

- The Member States where it is anticipated that the trial will be conducted.

After submission of the EudraCT Number form, I received an e-mail with the number assigned to the Clinical Trial, which had the format YYYY-NNNNNN-CC, where YYYY is the year the number was issued; NNNNNN is a six digit sequential number, and CC is a check digit (23).

At EudraCT website, the filing of the XML file is also performed. This is a form with several questions related to the Clinical Trial essentials for the submission of a Clinical Trial application to the competent authorities and to the ethics committees. XML file is in a specific format that can only be open at EudraCT website, however it also enables to save the information in PDF format.

The XML complies all the CT's information required by the authorities to assess the study and to enter the details of the trial into the EudraCT database, as required at CT directive 2001/20/EC (24). More specifically, it contains information regarding the trial and its Sponsor identification and also information about medication, target indication and population, the selected sites and investigators.

The filing of the XML file is a simple but extended process. The form is composed by10 sections, each one composed by a variable group of questions. Several questions are dependent of one another, i.e., according to the answer given we can have less or more questions to answer. To facilitate the process and to help the filing, the site raises alerts when the information is not correct or consistent. It only allow us to submit a section of the form when all the queries raised are solved.

### 3.2.2 Studies' Submission

After the development, revision and approval of all the relevant documents, the next step is the submission of an application to the CA. For the initiation of a Clinical Trial or a Clinical Study with Medical Devices, the application must be submitted to INFARMED, CEIC, CNPD and Study's Sites Administration Boards. Regarding Non-Interventional Studies, the application just needs to be submitted to CNPD, Study's Sites Administration Boards and Local Ethics Committees.

CNPD submission is accomplished electronically, via CNPD website (www.cnpd.pt) by completing a form with the requested information related to the Investigational Study. During the internship period, DATAMEDICA performed several CNPD submissions, therefore completing CNPD's form in order to submit clinical studies was one of the tasks that I performed at DATAMEDICA. Application assessment by CNPD focuses on the management of sensitive personal data, such as personnel and clinical data. Therefore, CNPD's application includes the following information:

- Identity and information of the study's Sponsor;
- Identity and contacts of the person/ entity responsible for data management;
- Type of data collected (philosophical convictions, ethnicity, private life, health data, genetic data, or other personal data);

- Type of data collection (direct, such as attendance, by phone, form, questionnaire, internet, or through indirect collection);
- Protocol synopsis;
- Informed Consent Form and Patient Information Sheet;
- Study's variables list/ URL of e-CRF.

After the submission, the responsible person, which can be the Study Monitor, must follow the approval process so that prompt attention can be given to any request for additional information, clarification or objections.

During my internship, I collected all the submission dates of applications to CNPD and the dates when DATAMEDICA received the final CNPD's authorization, to allow me to calculate the mean time obtained between these two points (submission and authorization), which is 138 days. Some applications included in this calculation had long evaluation process due to the raise of questions by CNPD. Even being a common willingness of the applicant to rapidly answer the questions, there is no limit period to give a reply, which is not the case when we talk about INFARMED or CEIC that have a legal limit period to the applicant reply questions raise during the evaluation process.

Regarding CEIC and INFARMED evaluation, the main focus is the quality of the scientific background of the protocol and the capacity of the investigational sites and investigators to conduct the study. According to the new Portuguese Law (Law No 21/2014), the request for a Clinical Study authorisation to INFARMED and to the Competent Ethics Committee (CEC) will be performed by the electronic platform RNEC – *Registo Nacional de Estudos Clínicos* (3). This platform is being designed to register and publicize clinical studies, allowing the interaction between different stakeholders, and with the main objective to facilitate the development of clinical investigation and enhance its disclosure to patients, health professionals and investigators. However, this platform is still under development and, therefore, the requests of clinical studies authorisations have not changed yet, and are still performed as described below:

CTs submission to INFARMED must follow the requirements described in "*Instructions for applicants for the request of a Clinical Trial Authorisation, Substantial Amendment submission, declaration of the end of a trial, SUSAR notification and annual safety report submission process – 16th June 2014"* and it should be performed according to "*Detailed guidance on the request to the competent authorities for authorisation of a Clinical Trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01)*".

INFARMED requests a set of documentation, from which the most relevant documents are:

- XML File, which summarize relevant information of the CT;
- Signed CT Protocol;
- Investigator's Brochure or Summary of Product Characteristic;

- List of all CTs involving the concerning Investigational Medicine Product (IMP);
- Financial memory;
- Insurance certificate.

This documentation must be saved on a CD-ROM according to a schematic organisation predefined by INFARMED in "*Instructions for Applicants"*.

The request for a CT authorisation to CEIC is similar to what was mentioned before. The request must comply with "*Instructions to applicants for the format and content of the request for a Clinical Trial authorisation process with medicinal products for human use, notification of amendments, adverse events notification and declaration of the end of Clinical Trial – June 2005*" and with CT-1 Guidance. For CEIC evaluation, the application submitted must be completed and the most relevant documents are the following:

- Signed CT Protocol;
- Experimental medicine circuit;
- Informed Consent Form and Patient Information Sheet;
- Patients' recruitment modality;
- Financial memory and final draft of the Financial Agreement and Clinical Trial Agreement;
- Ethical evaluation from the Coordinator Investigator;
- Authorisation from the Head of Department/ Service;
- Declaration regarding study site conditions and study team constitution, and declaration from the Head of Pharmaceutical Services certifying service's conditions to conduct the study;
- *Curriculum Vitae* (CV) of the Coordinator Investigator and of all the PIs.

As the submission to INFARMED, CEIC submission must be delivered in a CD-ROM format saved according to a schematic organization defined by CEIC in "*Instructions for Applicants"*.

During the evaluation process, INFARMED and CEIC may raise questions and the CRA must inform the Sponsor of the situation. A response to the authorities must be sent as soon as possible.

Nevertheless, the final authorisation to start the Clinical Study at a specific investigational site depends on the site Administration Board's approval.

Furthermore, the selection of the clinical sites is another important process because the centres are crucial for performing the study: they conduct the study according with the Protocol and create precise and reproducible clinical data in a timely and safe manner. Besides assessing Investigators' qualifications regarding education, training and experience through their CVs, the suitability of sites' material, human resources, infrastructures and population should be evaluated. Centres' selection depends on study protocol complexity, types of procedures required, availability of experienced staff, budgeting issues and, sometimes, on previous knowledge of centres' performance (25).

DATAMEDICA collaborates with a large range of public and private health institutions in the scope of Clinical Research. During the internship, I could observe the differences between studies' centres. Some centres, like big hospitals or specialised clinics, have a larger team allocated just for the coordination of clinical studies conducted at their centre and they give support to the study team by assisting on study visits schedule, aid on getting the collaboration of the different departments involved, help on filing of the CRF and in adverse events report or by recording study medicines' administration and coordinating patient' visits schedules. Also, this team provides aid to the CRA on the elaboration of feasibility surveys before sites' selection, on the contact with the departments involved in the study, on the elaboration of the Clinical Trial and financial agreements, on the collection of relevant documents, and facilitating monitoring visits and the conduction of Source Data Verification (SDV). Furthermore, in these centres, the administrative bureaucracy is better defined and works like a "well-oiled machine", once there are checklists that define what must be submitted to the sites' Administration Boards. There are established templates to be completed during studies' submission, and each sites' departments/ services also have their own templates and specific procedures. A good example is the pharmacy, where the reception, dispense, return, accountability and destruction of medication take place, which are crucial steps and, therefore, are tightly controlled by the Sponsor and also by the centres' pharmacy staff.

However, in some cases, such as in *Unidades de Saúde Familiares* (USFs) or small hospitals, that still not conduct clinical studies regularly, the Sponsor or the monitor directly contacts with the study team and the investigators are responsible to collect relevant documentation, submit the Clinical Study to the Administration Board and to manage the collaboration between all the sites' departments and between study team, besides conducting and complying with the Protocol.

The request for authorisation of a Clinical Study to a centre's Administration Board is a case-by-case process and must follow the centre's specific requirements. If the site does not have specified requirements for submission, the process must contain all the relevant documentation to support the evaluation process by the administration board, such as Clinical Study Protocol, ICF and PIS, CRF, authorisation letters of INFARMED and CNPD, favourable opinion letter of CEIC, head of department authorisation letter, CVs of PI and sub-investigators, draft of financial agreement and insurance certificate.

Site Initiation Visit (SIV) and inclusion of study participants into a Clinical Study must only be performed after all the approvals are in place, either received by the Sponsor or by its representative, namely, a CRO.

While supporting Clinical Operations unit, I have noticed two different dimensions: clinical studies in which the Sponsor is a multinational entity and where the study will be conducted in other countries besides Portugal; and clinical studies sponsored by a small Portuguese or Iberian entity and where the study will only be conducted in Portugal. Regarding the first ones, the Sponsor has a submission pack already prepared and the CRO only has to adapt some documentation to the

national law, language and scope, such as Study Synopsis, XML File and documentation that will be given to the participants, besides organizing the documentation that will be submitted to INFARMED and CEIC according to their own "*Instructions for Applicants"*. When given support to a national entity, the CRO must help the Sponsor regarding documentation collection, identifying the necessary documents or collecting it proactively.

The agreement of the insurance certificate is a legal requirement for the conduction of Clinical Trials and represents a very expensive item. Due to the lack of knowledge on the conduction of CTs, small companies do not know how to achieve the insurance and do not understand why it is so expensive.

In addition, DATAMEDICA's CRAs have faced some difficulties during a CT submission and implementation at a USF, because this facility does not have the same characteristics as a Hospital. A good example of these problems is the lack of a pharmaceutical service at the USF, which is a requirement to CT´s conduction, according to Law No 21/2014 to receive, storage, dispense, collect and destruct/ return the study medication. To pass through this situation, the study medication can be delivered to a qualified pharmaceutical service such as a local pharmacy. As similar to hospital pharmacies involved on a CT, the local pharmacy must have a qualified pharmaceutical responsible to receive, dispense, control and register the medication, a restrict access to the local of archiving study documentation and a fridge/ cabinet to storage the medication with a system that register the storage conditions (temperature and humidity).

Financial Agreements are also difficult to create. The discussion between all the involved parts is time consuming. CROs struggle with more difficulties when creating financial agreements in the scope of an IIS due to the lack of regulation for this type of studies and when performing financial agreements with USFs. In these specific centres, it is frequent the absence of a template that specifies the site requisites and there is no support documentation that assists the submission process.

### 3.2.3 Submission of Substantial and Non-Substantial Amendments

During the internship, I supported the submission of substantial and non-substantial amendments. The performance of amendments regarding the Clinical Study after its beginning is allowed according to the European Regulation and National Law (3, 26). A CT amendment may arise from alterations of the protocol or due to new scientific information that support the study. Amendments are classified as substantial when they have a significant impact on the safety of the participants, on the scientific value of the study, on the conduction/ management of the study or on the quality and/ or safety of any IMP used in the study. If none of these criteria is met, the amendment is classified as non-substantial (27).

During the internship, I performed, with the other CRAs, the notification of non-substantial and substantial amendments to INFARMED and CEIC. For both tasks, I helped on the elaboration of the notification letter, in which the alterations performed as well as the reasons were explained. The substantial amendment represented a bigger obstacle because it required the comprehension of the Clinical Trial and the identification of the alterations performed because the Sponsor did not send an alterations track. In this amendment, new information regarding IMP's pharmacokinetic enabled the alteration of the principal objective, the creation of a new study group, the increase of the sample size, the modification of eligibility criteria and of the study's procedures. Due to these modifications a new version of the Protocol, of the IB's, of the PIS and of ICF was created. The application submitted to CEIC and INFARMED included these new documents and a cover letter, in which the alterations were identified and explained.

## 3.3 Monitoring Activities

Studies' monitoring is a GCP and legal requirement (3, 8). This activity is important to assess the progress of the study at a specific centre and to ensure the complete adherence to the latest approved version of the Protocol/ Amendment(s), the quality of the data and the maintenance of the rights, safety and well-being of the participants. Also, the monitoring visits assess the compliance with ICH GCPs, relevant SOPs and applicable regulatory requirements. Monitors should also verify if the study data are in accordance with source documents and if each data is attributable to a real patient, legible, contemporary, original, accurate, complete, consistent enduring and available when necessary. Furthermore, the Monitors must be the link of communication between the Sponsor and the study's centres and team (8).

During the internship, DATAMEDICA performed monitoring activities mainly for oncology clinical studies and non-interventional studies. The **Erro! A origem da referência não foi encontrada.** shows the number of monitoring activities performed by me during the internship and the Table 2 summarizes the specific tasks that I performed in each one of them. However, I did not had the opportunity to perform in-house monitoring activities nor to support study team in tasks such as IMP management, subjects' recruitment, and procedures' schedules. I've noticed from the work of my colleagues that it is really important to have a good documentation support to assure the efficient response to the study team's questions.

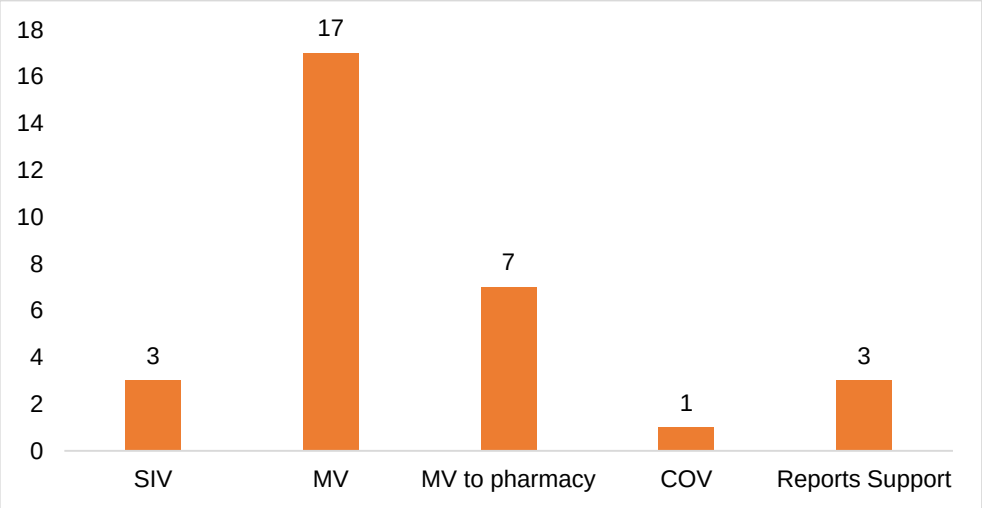


**Figure 5.** Number of monitoring activities performed during my internship

**Table 2.** Specific monitoring tasks developed by me during the internship

| Monitoring Activity | Specific tasks performed/ assisted |
|---|---|
| SIV | • Protocol training.<br>• Preparation of study presentations in the centre's perspective.<br>• Preparation and revision of Study Files: impression and archive of documents, missing documents identification.<br>• Training in Sponsor's SOPs. |
| MV | • Elaboration of documents designed for medication management by CRA in-house, for MV scheduling and for study team's support regarding visits and procedures.<br>• Revision of Study Files: verify the presence of ICFs; assess document logs regarding precision, consistency, completeness; revision and collection of essential documents.<br>• SDV of CRF.<br>• Adverse Events (AEs) and Serious Adverse Events (SAEs) report revision.<br>• Assessment of the need to perform a new training to the study's team.<br>• Verification if correction of findings of previous MVs were performed.<br>• Actualisation of periodic status of the study. |
| MV at Pharmacy | • Revision of a Pharmacy File (PF): verification of shipping, receipt, temperature logs, drug accountability and destruction/ return documentation.<br>• Revision with study team of the preparation and dispense procedures. |
| Monitoring visits report | • Support on the resolution of queries raised after report revision. |
| COV | • Revision of Study Files: impression and archive of documents, missing documents' identification, verify the presence of CVs; assess document logs regarding precision, consistency, completeness; revision and collection of essential documents.<br>• Medication accountability.<br>• Preparation and schedule of medication return. |

In the following subsections, each monitoring activity mentioned before and the specific tasks related will be detailed.

### 3.3.1 Co Monitoring Visits

During my internship at DATAMEDICA, I had the opportunity to follow other DATAMEDICA's CRAs in several monitoring visits to the study centres. I had the opportunity to be present at Site Monitoring Visits (SIVs), to help study responsible CRA in the conduction of periodic Monitoring Visits (MVs) and to attend a Close-Out Monitoring Visit (COV) to a centre that had not recruited any participants. In this chapter, I will describe the activities performed in this scope.

Before any of the described activities, DATAMEDICA's CRAs were trained (self-training or according with Sponsor requirements) in the Sponsor's SOPs, in the Protocol and in the study's

objectives. We also needed to be aware of the written ICF and of any other written information to be delivered to the participants (8).

#### *3.3.1.1 Site Initiation Visits*

The SIV is performed before patients' recruitment and its main objective is to prepare the centre for study conduction. In some centres, it is possible to schedule a meeting with all the study team, however, due to schedules' incompatibility, the CRA must go through all the Hospital Services involved in the study. I attended to a SIV that lasted two days due to the huge number of Hospital Services involved (medical oncology, cardiology, pharmacy, radiology, pathological anatomy, clinical laboratory, day hospital, and nursing) and it was not possible to coordinate a meeting with all the team members together. Therefore, the CRA needed to go to all the Hospital Services. In some centres, I have noticed a limited availability of health professionals in the scheduled visits.

In other SIVs that I attend to, the centre was only considered open when the Principal Investigator (PI) received the Green Light Form, which is sent after an evaluation by the Sponsor of the capacity of the centre and the study team to conduct the study through assessment of documentation sent by the CRA, such as INFARMED, Ethics Committee and site Administration Board's approvals, signed Clinical Trial's Agreement, CVs of the Investigators and of the Head of Laboratory, as well as Laboratory Certification, and other relevant documents.

Besides CRA's training, SIV's preparation includes the development of a presentation (or the adaptation of a presentation sent by the Sponsor) and the creation of study files: Trial Master File (TMF), Investigator Study File (ISF) and Pharmacy File (PF) and revision of Essential Documentation, such as Financial Disclosure, CVs, Sources Data Report, Acknowledgment of Receipt (AoR) for Protocol and Investigator Brochure (IB), and Monitoring Log, assuring that all the relevant documents are well and accordingly archived.

During the SIV, the Study's Protocol must be reviewed and discussed with the study's team, mainly focusing on eligibility criteria, study´s design and procedures. Training of study's team should include the completion of the CRF and the procedures for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs). Team responsibilities should also be discussed, especially PI's, as well as the monitoring plan (28). Moreover, at the Pharmacy, the specifications concerning reception, storage, handling and return/ destruction of the medication sent by the Sponsor should be discussed. Furthermore, it is relevant to inform the study's team regarding the other study centres that will be included, patient's recruitment at the time in Portugal and, if applicable, in other countries.

#### *3.3.1.2 Monitoring Visits*

Periodic Monitoring Visits (MV) are performed after patient's recruitment at the centre and are scheduled as defined on the monitoring plan, which also specifies the percentage of SDV that should be done by the CRA at each MV.

Before MV's conduction is essential to prepare it. Basically, during the internship, I prepared monitoring visits by starting to identify what was done at the last visit. After the identification of which patients' visits were previously monitored, I went to the CRF to verify which visits occurred since then and that must be monitored. Also, I go back to pending's issues from last MV registered in the MV's report and verify if they were already corrected. A checklist of outstanding issues that must be verified during MV is also prepared, to avoid forgetting any relevant points.

Through the internship, I was able to witness an inadequate support from the Investigators at Hospitals regarding the MV. Besides the pharmacy, where the pharmacist helps the CRA during the visit, monitoring activities are also performed in the company of the Study Coordinator (SC) and, due to his/ hers limited availability, the Investigator only appears when it is absolutely necessary to add or change any information on patients' clinical process or when it is necessary to sign any documents. Important tasks to the study conduction are also delegated to the SC, as the filing of the CRF. Therefore, SCs are important elements of the study team, in whom Investigators' responsibilities are delegated and, in many occasions, are approached to clarify any issue from the protocol instead of Investigator.

Source data is all the information necessary for the reconstruction and assessment of the Clinical Trial's conduction and is recorded in original registers or through authenticated copies of the original ones, defined as source documents. SDV is a confirmation process that assesses if the data collected on the CRF correctly reflect the data registered at original documents defined at the SIV as source documents. These documents can be patient's clinical process, laboratory results' reports, patient's diary, pharmacy's registries, exams' reports and, in some cases, CRF could be a source data document if the information is directly inserted on it. CRF as a source data is acceptable only if the information in question would not usually be entered as medical records in clinical practice, and if the knowledge of such information is not required by the Investigator or other health professional who concurrently/ subsequently treat the study's participant (25, 29, 30).

The extension of SDV is defined on the monitoring plan and depends on several factors, such as the phase of the Clinical Trial, the quantity of data, human resources and their availability, Investigator´s research experience, etc. One hundred per cent (100%) SDV could be a valid approach, mainly when the number of subjects at a trial centre is small and the CRA can verify all the data inserted on the CRF during a MV. However, when this approach is not feasible, it is important to define which is the critical information to the study and to the final results, namely primary efficacy endpoint, eligibility criteria, visits' dates, adverse events, concomitant medication and medication dispense, retrieval and accountability (31).

There are two methodologies to perform a SDV: by direct verification, in which the monitors have direct access to patient's clinical process; and by indirect verification, in which Investigator answers to the Monitor's specific questions regarding patients' data. CEIC allows the performance of SDV by a limited direct verification and the methodology to perform this verification is described at CEIC's guide "*Acesso aos dados do processo clínico dos participantes em ensaios clínicos pelos monitores*" (30).

Besides SDV, the monitor must review IF and PF during MVs in order to evaluate the documents and their archive. In the several MVs that I assisted, during the course of files' revision, the most common findings observed were: missing CVs of study's team or not updated after inclusion of new staff, insurance not updated and without validity date, originals documents' archive instead of copies, missing Clinical Trial Agreement or Study's Protocol versions, and so on.

It must be reinforced during a MV that whenever the study team changes, the CRA must be informed, and the Investigator or SCs should be asked if it did.

Besides SDV, I also performed medication's accountability and destruction during MVs. Drug's accountability is essential to monitor patients' compliance with the study medication and to assure the integrity of the clinical data. Noncompliance compromises patients' safety and affects the quality and acceptability of study's results. Therefore, drug accountability is a requirement of GCP for any trial that uses study-supplied medication. Correct drug accountability includes the evaluation of drug reception, storage, handling, dispensing, administration and return. To allow this assessment to be completed and accurate records must be well archived. Also the return or disposal of unused medication must be correctly documented (32).

Regarding the storage of study's medication, the CRA must confirm if the storage is in a securely locked area with temperature/humidity control. Therefore, in MVs, CRAs should require access to temperature and humidity logs to verify if any drastic alteration of storage environment that could impact quality of medication occurred. During MVs, CRA also check the dispensing of medication, which has to be according to study protocol and can only be provided to study participants. Before drug's return or disposal, counting of the used and unused medication is required to verify patients' compliance. During the MVs, I performed drug's accountability of pills and liquid ampoules and also performed the accountability verification made by the responsible to this task, who is normally the pharmacist. The documentation of all these processes is mandatory for the correct accountability and reconciliation of medication. Accurate records are essential to assure that medication was dispensed to the participants according to the study's protocol, to verify patient's compliance and data validity.

#### *3.3.1.3 Close-Out Visits*

A Close-Out Visit (COV) is the last monitoring visit performed at the study's centre. This visit aims to discuss with the Investigator the procedures that will follow the end of the study, to ensure that all activities required for centre close-out are performed and completed, that the copies of essential documents are correctly archived and that all study's materials were collected from the centre and returned to the Sponsor (8). The correct archiving of documentation is essential because it makes documents accessible in the future if needed for regulatory reasons, allowing the Sponsor or the Competent Authorities to reconstruct the study at the centre and to assess if the study was conducted in accordance with the Study's Protocol and with applicable laws and regulations.

These visits normally occur when there are no participants being followed at the centre and when all the AEs/SAEs queries (data clarification) are resolved and completed. However, I assisted a COV of a centre that was conducted because study team have not recruited any study participant during the recruitment period.

The COV must be confirmed with the Principal Investigator and the date and time and who will attend the meeting should be determined. In the COV that I attend, the PI was on maternity leave and her functions were delegated to a, therefore the meeting was only attended by the Sub-Investigator and by the Pharmacy's responsible.

During the visit, the study materials, namely the CRF files, were collected to be sent to the Sponsor and the Investigator File (IF) was reviewed and checked to ensure the correct archiving of essential documents, such as delegation log and screening log, ICF, patients' screening and enrolment log (which were not applicable at the COV that I attend to). During IF revision, duplicates and unnecessary copies should be removed, along as paper clips and staples, the index must be updated and note to files must be added if any section is not applicable or if documents are missing or wrongly archived in another file. Commonly, the IF must contain the original documents of the ICF, subjects' log, visits' log, follow-up letters and material and medication AoR. However, the last one could be archived at the PF. The originals of the signatures' pages of study's Protocol, CVs, laboratory certificates and delegation log must be collected and their copies must be archived. Nevertheless, each Sponsor must have is only requirements defined by SOPs, therefore, it is important to review Sponsor's SOPs before each visit (8).

It is also important to verify if all the AEs and SAEs were adequately reported, followed-up and documented. The discussion of the Final Study Report and publication plans and scheduling, along with the clarification of roles and responsibilities must also take place.

#### *3.3.1.4 Monitoring Visit Reports*

After any type of MV, a report should be done as soon as possible, when the information is still clear and can easily be remembered. This time period is usually defined by Sponsor's SOPs or, in their absence, by DATAMEDICA's. DATAMEDICA has a monitoring visit report's template to be used and the related SOP defines a 10 days period to the development and revision of the report.

The report must identify the study, MV date, the centre in which the visit was conducted and the personnel that attended the visit. A brief resume of study status on the centre can be done, approaching target recruitment number, number of participants screened, recruited, completed and withdraw. The report must also addresses the following themes: Study's Team (any change in the staff, new members' training, functions' delegation), Investigational Products (adequate storage, quantity, documentation of receipt, usage and return, expiry date, adequate dispense and correct use), CRF (accurately record data, consistent with source documents, correct documentation of concomitant medication, intercurrent illness, missing tests or examination, withdrawal situations), Protocol Deviations (ineligible participants' inclusion, identification and report of protocol's deviations), AEs (AEs and SAEs' report) and Study Files (archive, maintenance, and essential documentation revision).

After submission of the report at the platform, the document must be sent for Sponsor's revision and, after this, questions can be raised to the CRA. When finished, the report is sent to the centre along with a follow-up letter that summarizes the visit and describes any critical findings or required action items. This letter should clearly identify all the significant findings, deviations, deficiencies, conclusions and outstanding issues to inform the study team and to help them to correct these issues.

To standardize the report preparation in international CTs, in which there are several CRAs, Sponsors often choose to create an online platform. This tool also helps to control the report's development and revision's times.

During the internship, I did not had the opportunity to develop a monitoring visit report since the beginning. However, after Sponsor's revision, I have corrected the queries and answered all the raised questions.

## 3.4 Data Management

Study's data covers all the information collected during the study conduction and should reflect what have occurred on its course. The quality of the data depends on the study design, the selection and the quality of the measures and of the measurements devices, as well as the experience, training, competence, and motivation of the study team responsible for taking and recording the measurements, and on the choice and quality of data capture, processing, storage and analysis (33). Consequently, a good results' analysis depends on the quality of the data.

Clinical Data Management (DM) activities represent a critical phase in clinical research, with the main objective to generate high-quality, reliable, and statistically sound results. DM is the process that covers all the phases of study's data collection, cleaning, and management DM activities include CRF design and annotation, database design, data entry, data validation, discrepancy management, data coding, data extraction, and database locking (34).

Before analysis, the quality of data should be assessed and the information contained must be changed into a format that are readily analysed and interpreted. The data must be accurate, which means that there are a correspondence between the collected data and the real values of the "phenomena" that is being measured; precise, which reflects the degree of detail of study's data; consistent, considering the level of concordance between real data and the data present at the database; complete, which expresses the rate of missing values at the database; and data must have integrity, that corresponds to data usability and soundness, characteristics that are influenced by data´s validity and completeness (33).

It is not possible to compare DM activities performed at DATAMEDICA in the scope of clinical studies performed within national territory and DM activities performed at a pharmaceutical industry or performed by a subcontracted entity in the scope of a multinational Clinical Study. Regarding the last ones, before collecting worldwide information and pool it together, data managers must take into account variability regarding culture and religion, medical practice, laboratory standards and units, classifications disease and standard treatment , drug's reactions, self-medication, drug's interactions to conceive a complete DM Plan (25).

A DM Plan should include a data origin flowchart, project's team list and the respective responsibilities, CRFs log-in sheet (that makes the correspondence between user log-in and investigator), data query sheet, audit sheet and results' documentation and a sample document for formal notification of database's closure. To create this document is necessary to have access to the protocol, CRF, relevant literature, log-in and tracking methods, file structures, codification rules, query handling procedures, required edition checklist, laboratory normal ranges and units, clinically significant ranges, timelines, quality control rules, error analysis and criteria to release and close-out the database (25).

The DM activities performed at DATAMEDICA during my internship, consisted on CRFs' design, databases' design, data entry, data coding, and databases' revision and locking. However, I did not had the opportunity to work with any DM software tool, also known as Clinical Data Management System (CDMS). Due to this, an audit trail of the data, which is a chronological record that documents a sequence of activities performed since initial data recording until data locking, was difficult to maintain and control. Audit control is an important tool, mainly for studies that are conducted during a long period or in which the study team changes frequently.

A CRF is a data collection tool, printed or electronic, used in clinical studies that support the record of all protocol-required information (8). The design of a CRF influences data collection, data entry and validation process as well as data management and statistical analysis. The characteristics of a well-designed CRF are that the CRF should be informative, structured and simple, and should allow the collection of legible, consistent, and valid data, with the aim to decrease the time to perform both the data entry and query generation and resolution. Therefore, data must be organized in a format that facilitates and simplifies filing of the blank spaces and posterior data management and analysis. Furthermore, the collection of unnecessary information and large amount of data should be avoid because it will result in wasted resources.

A CRF must have headers and footers with elements that identify the Sponsor, the Study's Protocol, the visit and the subject in question, CRF version and date, and page identification/ numbers. These informative features provide a brief description of the study and the schedule of assessments allowing the identification of the correct CRF, preventing the use of an incorrect page or version (35).

When designing CRF layout, it is important to focus on the user, on the one who will perform data entry, and classify the data regarding time dependence. Information collected at a specific moment in time is called Non-time dependent data, such as demographics information and medical history. Time-dependent data is information recorded repeatedly over the study, such as vital signs collected at several study visits. Information collected over the study but not related to a specific visit is cumulative data and adverse events and concomitant medications are good examples. Usually, non-time dependent and time-dependent data are recorded in per visits pages of the CRF and cumulative data is recorded in cumulative logs, in which specific pages are structured just for this information (36).

DATAMEDICA has developed printed CRFs and, along with outsourced programmers, electronic CRFs. Both approaches have pros and cons. Paper CRFs are a better option for small studies. However, electronic forms are favourable because they are less time-consuming, while reducing the probability of entry errors. Also, audit trail of the data is easily performed and repetitive data, such as study identification, participant number or visit number, can be generated automatically by the system. Electronic CRFs allow the connection of different pages of the CRF and prior definition of data validation rules, which are useful tools during database cleaning performed along the study

duration, and did not require data entry because it allows the data's automatic exportation to an informatics application previously defined, avoiding data entry errors. Regarding data cleaning, the activities may be performed during study conduction, which reduces query resolution's time due to a faster communication between the data manager, the monitor and the study's team as well as timely database lock. Also, electronic CRFs enable the performance of in-house monitoring, in which the CRA verify data outside the study's site. Yet, electronic CRFs require adequate and available on-site technology, training and motivation of study's team, maintenance of the software and a higher investment.

In summary, CRF's development is a process that must end with a simple form or with a set of forms. During the internship, I had the opportunity to create paper CRFs and documents that supported electronic CRFs' development. However, I did not had the chance to accompany the electronic CRF's development along with the informatics as well as its validation. To keep the form simple and still collect all the required information is a complex task, as well as the comprehension and identification of potential connections between electronic CRF pages.

Data entry is a relevant step between data collection and database cleaning and statistical analysis. The introduction of information in the database is a time consuming activity and requires many human resources when the Clients want to entry a large quantity of data in a limited time period. At the internship, during the data entry of paper CRFs, it was possible to detect some relevant points that I have taken into account during subsequent CRFs' design:

- Use of consistent formats and font style and size;
- Use of clear and concise questions and instructions;
- Use of visual clues that indicate place and format of the data to be recorded;
- Use of check boxes whenever appropriate;
- Use of thick lines to indicate where to enter the answer and to separate columns;
- Give detailed guidance in bold or italicised;
- Minimise free text answers and use precoded answers, such as yes/ no, male/ female, severity of AEs, administration mode, etc.;
- Specify the unit of measurement and indicate the number of decimal places required;
- Use standard format throughout the CRF, such as data format.

The revision of a database includes the identification of missing CRF pages, missing visits or missing values, the confirmation that the screening/ randomisation numbers are given sequentially; the evaluation if all the blanks spaces are properly filled; the clarification of all text items, such as adverse events, concomitant medications, physical examinations, ECG and others; the verification of drug's dispense and return (25).

Database's cleaning aims both to identify the errors that occurred during data collection and data entry and to correct them or minimize their impact on study's results. Due to the great impact of data handling on the data quality and study results, database cleaning is an important task,

however, it receives less attention in GCPs and in Data Management Guidelines. There are gaps of knowledge about good methodologies and standards to apply in this activity, important to separate data editing from data manipulation. Some useful techniques for data cleaning are statistical outlier's detection and handling of missing data. However, little focus has been given to the treatment of missing data (37). During the internship, I helped the biostatistician performing database cleaning of a 6-year study that included more than 1.300 patients. Due to access constraints to CRF online platform and to the handover of several study's CRAs, some data were missing and some data disparities were find. Besides the access to partial source documents, not all the missing values were completed, which has reduced the quality of the data.

Some missing values were related to the alteration of CRF's baseline form after the recruitment period has closed. Site's study team were not correctly updated by the study's monitor and was induced in error by the information of completeness status of the form which did not reflected CRF's alteration. Therefore, the new data were not introduced in the CRF. In this particular study, an audit trail was essential to really understand the conduction of the study and all the alterations and measures implemented.

## 3.5 Advisory Boards

An advisory board is a meeting aimed to achieve a non-binding consensus regarding a specific topic. These meetings should be performed in a neutral space and/ or in an informal environment (like a hotel room), once that allows a much more free expression of opinions, giving more flexibility to the structure and management of the event. It is important to point out that advisory boards do not have the authority to create legal binding decisions, and, therefore, are mainly instructive.

First, when planning an advisory board, a clear and well-defined purpose should be established, with the final purpose to attain fully developed opinions and valuable recommendations. This purpose must be based on clinical needs. Second, the right experts should be invited. The selection of the experts should take into account their education, training and experience on the topic that is being discussed. Also, the group of experts must be representative, in order to capture all the spectrum of opinions. The meeting's moderator must be capable of impartially conduct the group on the discussion theme, controlling each argumentation time and moving forward towards the objective, aiming to enhance effectiveness. Moreover, before the advisory board, a meeting agenda describing the points that will be discussed should be prepared and sent to all the participants, also aiming at achieving the predetermined purpose. The presentations to guide the meeting must be didactic and adequate to the education level of the experts, to the theme and to the time available (38).

Besides the logistic part, advisory boards or expert panels or consensus meetings must be implemented in compliance with "Code of Ethics for Promotion Practices of the Pharmaceutical Industry and Interaction with Health Care Professionals and Institutions, Organizations or Associations Comprising Health Care Professionals" of APIFARMA (*Associação Portuguesa da Indústria Farmacêutica*).

Meetings with health professionals are essential for the development and improvement of health care, new medicines and technologies. Once there is a possibility of influenced decisions the conduction of the meeting should be the most objective possible so that bias can be avoided. For this purpose, APIFARMA developed the Code of Ethics previously mentioned. Chapter three defines the requirements to conduct promotional, scientific and educational venues regarding event venue and hospitality. In all events supported by DATAMEDICA, the venue was adequate and the meetings was not a place with leisure, entertainment or sport purposes. The hospitality provided by the Client was limited to travel, meals and registration costs (39).

DATAMEDICA was hired to support and assist in the organization of two advisory boards about multiple sclerosis and performed the corresponding reports. In these reports, all the items discussed, all the opinions stated and all the disagreement points were thoroughly described.

I took part in one of these advisory boards and, before the meeting, a self-training on the disease (multiple sclerosis) and available treatments has proved to be quite important. This autonomous

study was critical to follow and understand the experts' discussion on the theme. In this project, I was responsible to:

- Collect relevant information regarding multiple sclerosis prior to the meeting,
- Attend to the advisory board and,
- Prepare the report.

The preparation of this report turned out to be very challenging due to the specificity of the theme. The audio recording of the advisory board turned out to be very useful for this activity. Even though it did not had a great audio quality, the main points discussed and the main ideas raised during the meeting were possible to extract.

Besides attending to one of the above mentioned advisory boards, I had also the opportunity to participate in a consensus meeting, where health professionals and others were consulted as experts. This one differed from the first ones because its main objective was to obtain a consensual information of an expert group to support investigational projects. During the internship, I assisted three expert's panels that were conducted to determine the most accurate and similar to reality data regarding clinical and budget inputs for pharmacoeconomic models, which were focused on cervical cancer screening strategies. In the next section, more information related to this project will be given.

## 3.6 Pharmacoeconomic Studies

Pharmacoeconomic study is an analytical tool used frequently to support the decision of financing and management of pharmaceutical medicines or health technologies by the health care system. Therefore, cost-benefit, cost-effectiveness, cost-minimisation, cost-utility and cost-of-illness analyses are useful to compare the pros and cons of different strategies, such as medicines, technologies or medical practices/ interventions. These evaluations allow generating valuable evidence that support the selection of the optimal allocation of limited resources (40). Pharmacoeconomic appraisals may be performed regarding several types of technologies, such as medicinal products, medical devices, diagnostic techniques, screening tools, surgical procedures, therapeutic technologies or systems of care (41).

**Table 3.** Summary of the most relevant pharmacoeconomic studies (42)

| **Pharmacoeconomic Studies** | |
|---|---|
| Cost-Benefit Analysis | Comparison of costs and benefits of two or more interventions. Outcomes are measured in monetary terms. |
| Cost-Effectiveness Analysis (CEA) | Comparison of costs and outcomes of two or more interventions. |
| Cost-Minimisation Analysis | Comparison of costs of interventions that provide the same outcome. |
| Cost-Utility Analysis | Comparison of the cost per Quality-Adjusted Life Year (QALY) for two or more interventions that provide diverse outcomes. |
| Budget Impact Analysis (BIA) | Evaluation of the expected alterations in the expenditure of a health care system after the adoption of a new intervention. |
| Cost-of-Illness Analysis | Analysis of the costs of a disease |

Pharmacoeconomic analysis can be divided in three phases:

- Scoping phase, in which the specific question to address is defined and the suitability of the analysis proposed is appraised. Also, critical issues are determined, such as target population and comparators.
- Assessment phase, which comprises a bibliographic revision of clinical evidence and an economic evaluation of the technology.
- Appraisal phase, the pharmacoeconomic analysis.

The design and performance of pharmacoeconomic studies may vary regarding the methodology used, even having the same economic basis. Therefore, in this report, the methodologies adopted by DATAMEDICA will be introduced.

During my internship DATAMEDICA performed two pharmacoeconomic analyses: Cost-Effectiveness Analysis (CEA) and Budget Impact Analysis (BIA), with the main objective to decide which screening strategy of cervical cancer was more cost-effective or had less budget impact. To perform these analyses, electronic models that focused on the disease in question and on different screening strategies were created. Also, several key features were defined during model setup:

- Choice of comparator(s). Medical practice was one of the strategies selected. However, the model also included other strategies defined by Portuguese Society of Gynaecology;
- Target population (age range, specific country or region, ...);
- Analysis perspective. Regarding INFARMED methodological guidelines and NICE guide documents, the perspective is the viewpoint from which the economic evaluation is performed. The most correct perspective is society perspective that covers the patient, his family, health professionals and payer entities (public or private);
- Time horizon, that should be sufficiently long to reflect all the potentially important differences between the technologies regarding health outcomes and costs (41, 42).

Clinical and costs inputs were not defined during model setup. Clinical inputs included epidemiologic data related to the disease, such as incidence, prevalence and progression/ regression of disease probabilities, and information related to the screening strategy (specificity and sensitivity). In this scope, costs inputs comprised office visits' costs, screening and diagnostic exams prices, and treatments expenditures.

Model inputs were validated by an expert panel, in which I participated, and included Clinical Trials' published data, published literature data, and data on file. For the success of the expert panel, a bibliographic revision was performed and a survey that summarised all the clinical data relevant as model inputs was developed. For this survey, I had to collect several data regarding clinical results of Clinical Studies and resume it in a tabular format for an easier comprehension and analysis.

During the expert panel, the relevant strategies to compare on the pharmacoeconomic analysis and the clinical and costs inputs to introduce on the model were discussed. A report to summarise the expert panel's conclusions was developed and the model was updated with the inputs discussed. The expert panel and the pharmacoeconomic analysis involving the mathematical models' results were aimed to scientific public release in a complex publication plan that will be mentioned in section 3.7 Medical Writing. However, it is important to specify the difference between both the communications (abstract or article). The model set-up was changed regarding start age for screening (at 25 or at 30 years old), screened population (Portuguese or a specific Portuguese region), different screening strategies in comparison, and colposcopy exams after the screening

execution (or not). Due to these variations, several comparisons and analysis were possible to perform and to divulgate to the scientific community.

## 3.7 Medical Writing

Medical writing is a transversal activity of Clinical Research that includes documents conception, management, review, approval and release. The activities developed by a Medical Writer are extremely important to the projects and to the company because their success depends on proper documentation of research plans and results release and on all the written records that supports them at any period (43).

Medical writing services include Clinical Research and Publication support. The first one comprises all the MW activities, such as the creation, translation or adaptation and revision of Study Protocols, Patient Informed Consents, Nurse Sheets, Cover Letters, Investigator Brochure and so one. It also includes the conception of Clinical Study Reports, which are developed according to ICH E3 "*Structure and Content of Clinical Study Reports*". It also includes the establishment of documentation quality management system-related which is important to assure an efficient work of the DATAMEDICA's team, namely Quality Manual, Standard Operating Procedures (SOPs) and Monitoring Plans. Publication support is a service directed to the conception of diverse publication forms: scientific journal articles, abstracts for conferences' submission, poster presentations and oral communications. Medical writing also gives support at the revision, bibliographies, citations or references' management, and at the adaptation of the documents' format according to specific directives.

During the internship, I had the opportunity to perform the following medical writing activities:

- Literature reviews;
- Development of Study Protocols, Patient Informed Consents, Nurse Sheets, Cover Letters;
- Conception of abstracts for Congresses' submission and, after approval, the related poster;
- Development of articles for submission to national and international journals;
- Support DATAMEDICA's Financial and Administrative Department creating the budget proposals according to Clients' requests or as a result of a Scientific Department brainstorming aimed to meet Clients' needs.

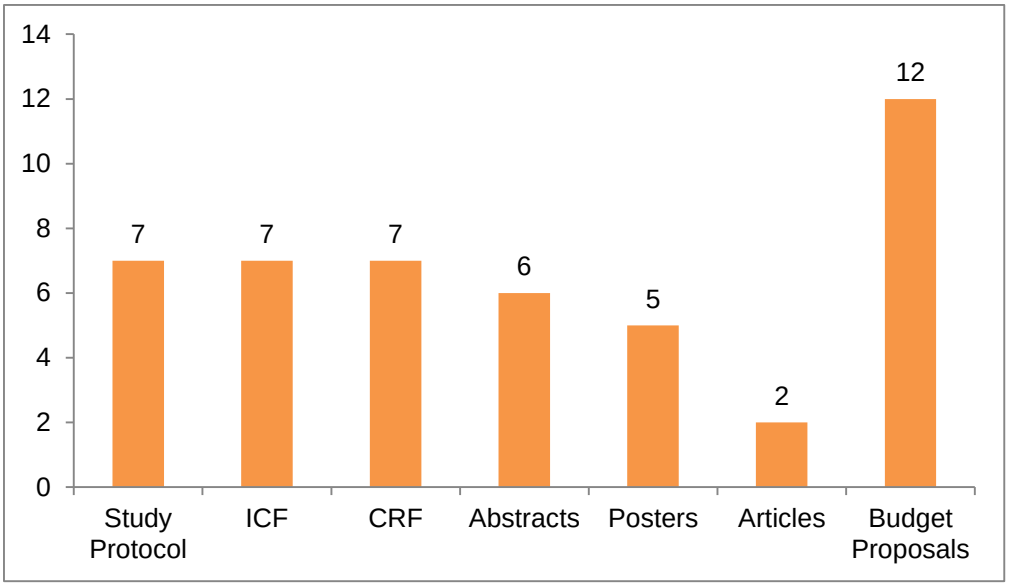


**Figure 6.** Number of MW activities performed during the internship

Literature revision is important to support a new Clinical Study and all the related documentation and equally to support a DATAMEDICA's service proposals for a new business opportunity. The attainment of theoretical knowledge is of a great importance to guarantee that DATAMEDICA's services met clients' requirements and main objectives.

Literature revision in DATAMEDICA is mainly performed through Pubmed Database and Clinical Trials Database (clinicaltrials.gov and clinicaltrialsregister.eu). Besides published review articles that give an overview on the theme, we also search for published clinical studies, undergoing Clinical Studies and authorities releases.

At services proposal development, literature revision is important to support the service to be provided and to justify the methodology that DATAMEDICA advocates. It is important to convince the client to allow DATAMEDICA to be responsible for the service needed. The implementation of team discussions and brainstorming meetings after bibliographic research and self-training on the theme is a good way to define the best methodology to accomplish a specific service or to achieve a certain result or to reach predefine objectives. During the internship, I had the opportunity to write budget proposals in diverse fields of Clinical Research, such as Clinical Studies, Pharmacovigilance, Medical Writing and Quality Management System, and also to participate in discussions over the methodologies that will be presented to the Client. This activity allowed me to understand the budget calculation process performed at DATAMEDICA.

Additionally, DATAMEDICA had MW activities that I was able to assist, support and perform by myself during. The most challenge one was the creation and revision of CT Protocols. Regarding Clinical Studies, table 4 summarizes the most relevant elements that should be address in a Protocol.

**Table 4.** Most relevant items to address in a Study Protocol and brief description of each one (8, 22)

| Protocol items | Brief description |
|---|---|
| *Administrative Information* | |
| Study title and code | Descriptive title and code, which allow to identify study design, population and methodology. |
| Roles, contacts and responsibilities | Names, affiliations, contact information and roles of Sponsor and Protocol contributors, such as Medical Coordinator, Biostatistics, CRO (if applicable). Name and contacts information of Coordinator Investigator, Monitor Responsible and Sponsor's Medical Expert.<br>Composition, roles and responsibilities of any committee defined to the study (if applicable). |
| *Introduction* | |
| Background, rationale and objectives | Description of the research objective and the justification for the conduction of the study.<br>Summary of relevant clinical and non-clinical studies and evaluation of benefits and risks due to the intervention. Explanation for choice of comparators (if applicable). |
| Trial design | Description of study design including study groups, type of trial (parallel, crossover, single group,...), allocation rate, framework (superiority, equivalence, non-inferiority, exploratory) (if applicable), study duration, participants eligibility and withdrawal criteria, study outcomes.<br>Use of schematic diagram to explain the study design. |
| Sample size | Estimated number of participants that should be enrolled to achieve study objectives. Clinical and statistical assumptions that supported the sample size calculation. |
| Study intervention(s) (if applicable) | Interventions for each study group. Description of the study intervention(s) and the dosage and dosage regimen. Criteria for discounting or modifying allocated interventions for a specific participant. Concomitant medication or care allowed and prohibited. |
| *Data Management and Statistics* | |
| Data collection methods | The identification of any data to be recorded directly on the CRFs. Methods for data collection and any related process to enhance data quality. Description of used tools (questionnaires, laboratory tests,...) and their reliability and validity (if applicable). |
| DM & Statistical analysis | Plans for data entry, coding, security and storage. Definition of analysis population. Statistical methods to handle missing data. Statistical methods to analyse primary and secondary outcomes. Subgroup's analyses. Timing of interim analysis. |
| *Ethics and Publication Considerations* | |
| Description of ethical considerations relating to the project. Plans to maintain and protect personal information. Person/ entity which will have access to the final trial database. Financial and other competing interests of the different stakeholders. Plans for communication of study results. | |

The creation of a Study Protocol should involve a multidisciplinary team work with qualified individuals such as physicians, Clinical Research methodology experts, biostatisticians, medical writers. As mentioned before, the Protocol must contain all the relevant information about the study in a simple and easily understandable way. The Protocol must maintain consistence in the entire document. I had the opportunity to review a complex Protocol generated by the Client, which had repeated information in an excessive way. This has difficult the document's revision process. Also, during the revision, several questions were raised to the Client due to initial discrepancies contained within the document.

When developing long documents, such as Study Protocols or Manuals, there are important tools that facilitate the writing, reading and understanding of the document such as cross-references, automatic numeration, table of contents, glossary of non-standard or ambiguous terms and a list of abbreviations and references. These tools also help the document's revision process, which must assess scientific accuracy, grammar, style inconsistencies, lack of clarity and other errors, as mentioned before.

After development of the Study Protocol, it is possibly to start the conception of Informed Consent Form (ICF) and other necessary documentation.

The ICF is the most important document for the protection of human subjects during their participation on clinical studies because it gives information regarding subjects' rights and duties, as well as possible risks and foreseeable adverse events. During the trial, the ICF also protects the Sponsor from legal consequences if the patient is harmed in any way.

The ICF consists of two documents: the Information Sheet and the Consent Form. Usually, they are considered as a pair of documents and not as separate ones. During the creation of an ICF, the following information should be included (8):

- Explanation that the Clinical Study is part of a research and describe its purposes;
- Treatment during the trial and the possibility for the occurrence of a randomised allocation to a study group;
- Study design and procedures that will be followed;
- Rights and duties of the participants;
- Experimental aspects of the trial;
- Expected risks for the participants as well as for embryo, foetus and nursed infants, and expected benefits of study participation;
- Alternative treatments for the participant and their side effects;
- Compensation and insurances for the participant if harmed;
- Voluntary participation and possibilities for refusal at any time;
- Open access to medical documents to the responsible monitors, auditors, Ethics Committees, Health Authorities;
- Data protection and confidentiality;
- Contact person/ entity in case of harm;
- Circumstances and reasons that can stop the participation or the study;
- Expected duration of subject participation;
- Approximate number of participants that will be included.

The ICF must be written in an understandable way to the subject and therefore, technical and medical jargon should not be used. The Consent Form must be signed and dated by the subject and by a person of the study team in the centre before any participation in the study (8).

Besides the development of study documents, DATAMEDICA also supported the preparation of articles, abstracts, posters and oral communications. During the establishment of key points to address in each document, it is necessary to obtain proper acknowledgment about the theme and proper input from the authors. I supported the preparation of a revision article, without a proper input from the Client/ Sponsor, once the manuscript objectives hadn't been previously defined. In other situation that I witnessed, the document was created, reviewed and changed without Client's input or consent. These entropies delays the development process and following submission, which would not happen if specific deadlines, communication and follow up meetings exist.

Abstracts creation process requires a good ability to synthesize. Each congress/ meeting has its own submission guidelines, specifying all the information that must be clearly stated, the number of words/ characters, and other relevant instructions. Abstracts main topics are: objectives, methods, results and conclusion. However, other topics could be required such as introduction and discussion. Regarding all of these sections, objectives, methods and results should receive greater emphasis, because these are the topics that explain what kind of research is being submitted.

During the internship, I prepared an abstract, in which the results of the BIA were displayed: "*Impacto Clínico e Económico de Diversas Estratégias para o Rastreio do Cancro do Colo do Útero"*. This abstract was accepted for poster presentation at the "*181ª Reunião da Sociedade Portuguesa de Ginecologia*" and received the best poster award. After this one, other abstract created by me was submitted to the "*13º Congresso Português de Ginecologia"* and it was accepted for oral communication. At the moment of the delivery of this report, a third abstract was submitted and accepted also for oral communication to the 30th International Papillomavirus Conference (HPV 2015). Usually, the submission process of an abstract is an easy task because the submission guidelines are very clear.

Posters' development start after receiving the confirmation of the acceptance of the abstract to be present as a poster at the Congress. At DATAMEDICA, posters are designed using PowerPoint and the first step is the definition of the correct proportions of the PowerPoint slide that must be according to the Congress's specifications, which is important to maintain the correct definition when saving the document as PDF. Simple fonts, such as Arial or Times New Roman, are of easily reading. When inserting images is important to assess its quality to make sure that they will not pixilated when impress. Others design features important to give a good appearance to the poster are the alignment of text boxes, pictures or graphs and the maintenance of a consistent spacing between sections and columns.

Posters are a helpful tool to simplify the rapid communication of a research to national or international population. However, it does not substitute an article publication, which is essential to specify all the relevant details of methodology and to discuss and explain the results in detail.

An article preparation is a more complicated process. The article must be correctly written to effectively communicate the research's data, information and underlying message. To achieve that,

it is advisable to use a simple, concise and specific title that correctly describes the content; avoid complicated jargon's use or a highly specialized language to experts of the area; exclude unnecessary details; avoid very long paragraphs and sentences and to use current literature (44).

During the internship, I supported an article development without knowing the target journal to publish and also an article development for a specific scientific journal. At the first case, the conception did not take into account any instructions. For the second one, the instructions for the preparation of a manuscript to submit at the Journal of Lower Genital Tract Disease were taken into account. Besides relevant ethic's considerations, this guideline defines word count limits, article's structure, references' format and other relevant specifications that help the Medical Writer in his chore (45).

Article's submission process is much more complicated than abstract's submission. The process of submission to the Journal of Lower Genital Tract Disease started two months before the delivery of this report and, at the moment, is still pending. The main obstacles are related to the collection of all the necessary documents to submit (Disclosure Form, Copyrights, Cover Letters, Submission Checklists, …) from the authors, as well as its correct filing.

## 3.8 Quality Management System

At the time of the beginning of my internship, DATAMEDICA's QMS was under an extensive revision process headed by a QA Manager specialist. Even not being the focus of my internship, I helped in the revision of DATAMEDICA's QMS.

According to ASQ Glossary, a Quality Management System (QMS) is a "*formalized system that documents the structure, responsibilities and procedures required to achieve effective quality management*" (46). Therefore, the QMS is a set of processes, procedures and policies necessary for the planning and execution of the diverse activities of an organisation. In Clinical Research, the QMS is a requirement for all Good Practices activities because it assures, in an efficient way, the compliance with regulatory requirements and standards, and allows the company to accomplish Client expectations, which gives the company a competitive advantage (47). Furthermore, an effective QMS allows process control improvement, wastes and costs reduction, as well as increase the profit and the company's market share. Furthermore, it involves all the collaborators and company's Management and facilitates staff training.

The QMS certification states that the products/ services delivered to the Client, are compliant with the relevant national and international regulations and standards, as well as the processes and the systems that support products/ services development. Certification is also an assurance to the target market and to the Clients all over the world. The certification of a QMS is assessed regarding "Quality Management Systems Requirements – ISO 9001:2008".

International Organisation for Standardization (ISO) is an independent, non-governmental organisation that develops international standard documents. Standard documents are made by experts of the area/ sector, through a consensus process (48). The implementation of ISO 9001 allows company's continuous improvement regarding mainly the QMS and processes and increases the capacity to deliver services that meet customer requirements and expectations. An efficient QMS enhance company's profitability and demonstrate the commitment to the service quality.

ISO 9001:2008 is based on eight quality management principles:

- Customer focus
- Leadership
- Involvement of people
- Process approach
- System approach
- Continual improvement
- Fact-based decision making, and
- Mutually beneficial supplier relationships

ISO 9001:2008 recommends a process approach. A process is any activity or a set of activities that use resources to transform specific inputs into specific outputs (46, 47). Process approach covers the identification and the systematic management of the processes allowing both the uniformity of tasks and their success. It also allows to easily identify which part of the process can be changed in order to improve its results. In this model, Clients are responsible to define the inputs requirements. Customers' satisfaction assessment and validation is essential for the continuous improvement of the QMS and of the Company. To sum it up, besides providing the product/ service to the Client, the QMS must address measurement analysis, continuous improvement and resources management.

"Quality Management Systems Requirements – ISO 9001:2008" defines six mandatory processes that must be documented as part of the company's QMS:

- Control of documents and records;
- Internal audits;
- Control of non-conformities;
- Corrective actions;
- Preventive actions (49).

Quality implementation and improvement requires a very close involvement of company's management regarding support and responsibility because this backing facilitates the involvement of the rest of the collaborators and allows us to have access to the resources needed in this process. However, at DATAMEDICA, QMS revision process could have been easier if DATAMEDICA's management involvement had been larger, which was inconsistent with the fact that QMS revision was a strategic decision of the company's Management, in order to define its objectives and continuously improve the services provided.

During the internship, I supported the Quality Management System in the revision of the company's organisational chart, which is a diagram that resumes the organisation structure, the relationships and the hierarchical positions of its departments and units. This diagram is important for the company because it allows to visualise the complete organisation of the Company. Due to the small size of DATAMEDICA, it was only structured a completed organisation diagram. The split of the cart in smaller charts for separate company's department occurs when the company is larger than DATAMEDICA. For this task, it was required to understand company's structure and the actual relationships between collaborators. At the top of the organisational chart, it is displayed the company's Administration Board, below which we can find other hierarchical positions. Lines indicate the relationships within the company and dashed lines indicate relationships with external suppliers or collaborators. However, organisational charts also have limitations once they do not provide information about the managerial style adopted by the company and they do not show all the relationships developed with and by the company, it only shows formal relations.

I also started to perform DATAMEDICA's Standard Operating Procedures (SOPs) revision. A SOP is a set of written instructions that guide a routine activity performed at the organisation. Therefore, SOPs provide the collaborators with the essential information to correctly perform each activity and, also, facilitate consistency in quality and efficiency of a service, even when occurs temporary or permanent personnel changes, while assuring compliance with organisational and legal requirements. Due to these reasons, SOPs are an integral part of a successful QMS. Besides detailing the work processes, they define responsibilities and timelines which are essential for the conduction of any activity, also stating the personnel qualifications necessary to perform the activity in question. SOPs success are influenced by their written quality and by the enforcement given by company's management to reinforce the importance of following SOPs.

To facilitate SOPs reading, they should be written in a concise and step-by-step format, using unambiguous and explicit information. Active voice and present verbal tense are recommended. The documents should be simple and short. Redundancy and overly length should be avoided. To illustrate the process, a flowchart is always a good choice (50).

The revision of area-specific SOPs is being performed by DATAMEDICA's collaborators responsible for the process because they are true experts, who actually perform the work or use the process. Therefore, they are the most capable to detail the process in such way that someone with limited knowledge or experience can successfully perform each task. The revision of Training SOP was delegated to me.

I did not performed a simple revision because it was necessary to adequate the SOP's scope to all the DATAMEDICA's departments/ units, increasing the old scope that was only focused on CRA's training. Besides a checklist that identify the essential training to give to a new collaborator or to refresh old ones, the documentation of the training must be performed and correctly archived. In clinical research field, adequate training in the Declaration of Helsinki, ICH GCP, European directives and regulations and national laws related to clinical studies are required. Additionally, DATAMEDICA's collaborators must be trained at the company's internal procedures. More specific training was adjusted according to the work position. For example, CRAs must perform protocol-specific and protocol-related training.

SOPs revision and adaptation process allowed me to exercise my knowledge regarding quality and my writing skills, while improving the efficiency of Company's procedures and the quality of services.

During the internship, I watched some faults that were committed due to the lack of an efficient QMS. One was the printing of the most recent budget proposals saved on DATAMEDICA's server to deliver to the Client. However, that was not the most recent document and it did not have the costs of the proposed services. The error was only noticed during the meeting with the Client. The corrected document was not saved on DATAMEDICA's server. It was archived only as an annex of emails exchanged within DATAMEDICA.

# 4. DISCUSSION

The next section will be a brief discussion of the relevant aspects of this training period, where the problems and challenges that I went through will be presented as well as all the positive and negative aspects identified. Therefore, I will make a reflection of the seven-month experience.

This internship was a very rich experience and in this report I try to describe all the projects and experiences in which I was engaged. Even showing the big amount of knowledge acquired during the internship, I cannot properly show in this the report all the effort given and that I put in all the activities performed. Several projects required extensive hard work and availability to perform additional off-work hours due to the difficulty of the activities or due to the tight timelines defined by the Client. However, it was always part of my learning process and I am grateful for the opportunity that was given to me and to the colleagues that have guide me during these 7 months with wisdom and patience.

I decided to perform my internship at a CRO because I believed that working for this stakeholder would be more beneficial to me. A CRO performs numerous services focused in all Clinical Research phases. As a small company DATAMEDICA was able to overcome my expectations because it was possible to learn and perform activities related to several Clinical Research areas. Therefore, besides the CRA focus of the internship, I gained experience in clinical studies conceptualization and development, pharmacoeconomic studies, data management, biostatistics, medical writing and QA.

As it is possible to understand through the reading of this report, my internship was not focused on a specific activity. Instead, I performed activities in all the areas in which DATAMEDICA had projects. This lead to a more enriching experience because the amount of knowledge collected was huge and the necessity to improve my soft and hard skills was higher, challenging me to always do better and pursuit higher results.

I am very fortunate to be involved in all the DATAMEDICA's projects once that allowed me to comprehend that I do not see myself as a CRA. Before the internship has started, I really wanted to perform CRA functions, however the idea that I have changed and I realize that this was not what I want to do in the future. I thought that CRA position was stimulating and also allowed to travel between many different sites and places, to know different people and that I would like to be out of the office instead of being bored if staying at the office all the time. Yet, I recognised that CRA activities are not so appealing.

Regarding the variety of activities performed during the internship, I was capable to see and act in different areas and I am now able to decide which activities I liked the most and that I would like to keep doing in the future. Nevertheless, this internship still leave me with the question of which activity I like the most, either to be involved in conception and development, or medical writing or QA activities. The first two are very stimulating and require continuous training and individual

improvement, as well as working data to obtain information to publish or to design clinical studies. Even though, I also like to perform QA activities because it allow to organise company's work and , consequently, my work as well, in an efficient way, which is important to me because I challenge myself through organisation and perfection and because it is difficult for me to understand the lack of work coherence and linkage within a company.

During the bachelor, master and extracurricular activities, I acquired extremely useful knowledge. Knowledge applicability covered all the tasks performed by me at DATAMEDICA, since budget proposals development to projects report. At the beginning of the internship, this was an individual motivation to perform the internship at a CRO and, nowadays, after ending my internship, I noticed that I was able to put into practice the knowledge acquired during my academic training and, when I had not learn the required information previously, I knew where to find it. The whole internship period had a learning component, which allowed me to increase my know-how and improve knowledge obtained at the university. Furthermore, I believe that the application of the theory is the better way to really understand it.

The first months of the internship were very difficult, not only due to the reason of being a new experience, but I felt also that I was not given the necessary and adequate support to start my activities in DATAMEDICA's. At first internship weeks, I thought that I would receive training in DATAMEDICA's procedures, ICH GCP and European and national regulatory framework of Clinical Trials, which did not happen. Autonomously, I searched DATAMEDICA's SOPs at office cabinets and files and I read SOPs that, as I found later, were not the updated documents. Also, the realisation of an activity that I never had performed before has seen as a terrifying situation because I did not felt the essential support of DATAMEDICA's Scientific Management. At this time, all the support was given by my colleagues and I rarely received Managers' feedback. However, due to human resources' changes, this panorama improved and, nowadays DATAMEDICA's employees work as a real team and the Manager's feedback is given equally either to individual achievements or to the committed mistakes. Therefore, the idea of performing a new activity is less frightening and more stimulating because we know that there will be the necessary aid when we do not know what to do and that our work will be reviewed and corrected if necessary, as well as the reasons for modifications are going to be explained.

Work in a CRO Full Service is a very demanding activity that requires good skills of communication, organization, attention, responsibility and mind flexibility. Communication is very important because a collaborator must know how to communicate with different professionals, such as Clients, health professionals, lay people or authorities' representatives and, therefore, we must be able to adapt the speech according to the target audience, while keeping the scientific information/ message correct. This was not an easy task for me and, at the beginning of the internship, it required a great effort from me. Nowadays, I have notice that I have more capacity to communicate, which is related to the interaction with a diverse range of professionals, and, also, to work on my difficulties with the help from DATAMEDICA's Managers.

My organization skills were improved due to the amount of projects, in which I was participating and, therefore, it was really important to have a methodical work and to keep a track of all the activities performed and to perform. Furthermore, the follow up of all DATAMEDICA's project enhanced my mind flexibility because during work it was frequently required the ability to jump between projects and rapidly answer specific questions about the project's status. Documents' revision and monitoring activities, such as the preparation of visits, made me more focused in the details. Autonomously, I improved time management and proactivity skills in this 7-month experience.

Besides time management, mind flexibility and organization, the amount of projects in which each collaborator was involved required a good activity planning, which is essential to prioritize tasks, activities and projects. Planning improves team efficiency, because it allows to save time, resources and energy and the team can be focused on urgent activities, and also assures alignment with the Clients and theirs requirements. However, planning should always be associated with flexibility and adaptability to new scenarios that require alteration to the prior plan.

The internship allowed me to understand the interactivity between the different departments to deliver the services requested by Clients. It was possible to verify that all the inputs were valuable and, therefore, should always be shared and, even more, everyone can make the difference, so everyone is important. I become very quickly a valid and productive member of the team in behalf of my rapidly adaptation and desire to learn. I noticed this because other team members started requiring my opinion and feedback very soon.

Multidisciplinary teams are difficult to manage, sometimes due to knowledge differences, others due to entropies related with personalities. Team building activities and transparent communication along with conflict management tools were important to diminish the occurrence of stressful situations between the team members and to allow the collaborators to grow as a team. Understandably, the lack of communication or mutual respect, poor planning, and lack of trust can result in undesirable outcomes that may have negative consequences over company's services.

Due to modifications of DATAMEDICA's resources, some projects were faced with less knowledge. However, for all of them, it was possible to correctly respond to the arise difficulties and to overcome all the obstacles. These situations were also important on the development of my skills because they improved searching competences and critical thinking, simultaneously with the capacity of dealing with problems and promptly solve them.

Repeated meetings with Clients are essential for the good conduction of the project. These meetings allow to understand the status of the project and to decide what to do next. However, I attended some unnecessary meetings, with the objective to perform Clients/ Investigators tasks instead of them. If DATAMEDICA's collaborators have not schedule the meeting, Clients/ Investigators would not carry out their tasks, which would delay the project timelines. Furthermore, projects' delays are seen by the Client has CRO's low commitment and they do not understand the

involvement of external factors that delay the activities, such as submission and evaluation's process, lack of answer by other involved parts or even lack of Client's feedback. To avoid misinterpretations and conflicts, a good communication with the Client is necessary and, to protect CRO's work, meetings and projects development should be always registered. During the internship, I developed the habit to write the summary of the meetings with the Client and delivery it to DATAMEDICA's management. If they considered it necessary, this summary was sent to the Client.

The interaction between CRO and Clients for potential future collaboration projects can be described as delicate at best. To maintenance old clients and acquisition of new ones is important to provide high-quality services at scheduled time. The satisfaction of a Client may bring new projects to DATAMEDICA. Also, a satisfied Client may reference DATAMEDICA to other companies as a good services' provider.

Regarding the activities performed in the scope of QA, I could realise that this is an enormous and very stimulating field. Maybe due to the enthusiasm of the QA Manager, I see a QMS has a "must have" for the correct and efficient work of a company. It maintains and improves efficiency in all the activities performed and it allows to implement tools that can identify gaps, flaws and possible processes that require improvement. Documentation of important information and document control are essential to avoid errors or forgetfulness of important tasks. Unfortunately, my participation in QA tasks was limited due to the necessity to develop other services and conduct other projects. I hope that in the future I may have other opportunities to work in QMS area and learn more about this area.

## 5. CONCLUSION

To conclude this report, I would say that the opportunity to conduct my internship at DATAMEDICA's was an important and enriching experience, considering all the activities performed and knowledge acquired. I was able to achieve all my objectives for the internship and play an active role in activities that can improve current clinical practice, such as Clinical Trials and advisory boards.

I finish my second year of master with the feeling that I have accomplished the majority of my proposed goals defined at the beginning of this journey. This unique experience allowed me to grow and become a competent professional and I can say with great certain that this year was the most enriching one of my academic life.

Every working day was full of new challenges and learning opportunities and we always made every efforts to end the day with the better quality service delivered to the Client.

I cannot identify a major focus of the internship, which I do not see as a bad thing. The possibility to attend and conduct different activities increased my hard and soft skills exponentially. The knowledge acquired during the internship covers all the health products cycle of life and I feel capable to perform any Clinical Research-related activity. However, I know that skills and knowledge can always be improved.

To sum this 7-month experience, the conduction of all the activities summarized in this report gave me all the background necessary to become a good professional in the clinical research area. I also understood that hard skills, such as writing, revision or statistical skills, can be learned and trained. For all competences, willingness to learn, repeated practice and experts' support are essential tools to understand and apply during work all the specificities for each activity.

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