Universidade de Aveiro Secção Autónoma das Ciências da Saúde

2011

TIAGO MONTEIRO DA COSTA CARVALHO FERREIRA

RELATÓRIO DE ESTÁGIO CURRICULAR NA NOVEXEM PORTUGAL, LDA

CURRICULAR TRAINING REPORT IN NOVEXEM PORTUGAL, LDA

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Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Doutora Teresa Almeida, directora-geral da Novexem Portugal, Lda e do Doutor Bruno Gago, professor assistente convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

I dedicate this work to my family and friends for all the support and good moments that made this possible.

o júri

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palavras-chave CRO, indústria farmacêutica, investigação clínica

resumo

As empresas da indústria farmacêutica (a Industria Farmacêutica ou os laboratórios farmacêuticos) têm vindo nos últimos anos a solicitar uma maior participação/parceria de Clinical Research Organizations (CROs), muito por falta de recursos próprios ou estratégia comercial, de forma a conseguirem uma agilidade temporal nos seus processos bem como poupança de recursos.

Hoje em dia, as CROs são consideradas como parte integrante e fundamental da investigação clínica e estão espalhadas um pouco por todo o mundo. São empresas multidisciplinares que fazem da diversidade de ofertas e soluções os seus pontos fortes.

O presente trabalho propõe relatar as diversas actividades desenvolvidas numa empresa de prestação de serviços na área da investigação clínica.

keywords CRO, clinical research, pharmaceutical industry

abstract

In recent years, pharmaceutical industry companies (Pharmaceutical Industry or Pharmaceutical Labs) have been requesting the participation of/partnership with CROs, mostly due to the lack of resources or business strategy in order to achieve a temporal flexibility in their processes, and also to save resources.
Nowadays, CROs are considered an integral and fundamental part of clinical research and they are scattered all over the world. These are multidisciplinary companies that make diversity of offers and solutions their main strengths.
The present work aims to report the various activities in a company providing services in clinical research.

List of abbreviations

ADR – Adverse Drug Reaction

AE – Adverse Event

bn - billion

CHMP – Committee for Medicinal Products for Human Use

CEIC – *Comissão de Ética para a Investigação Clínica*

CIOMS – Council for International Organizations of Medical Sciences

CNPD – *Comissão Nacional de Protecção de Dados* – National Comission for Data Protection

CRA – Clinical Research Associate

CRF – Case Report Form

CRO – Clinical Research Organization

CTA – Clinical Trial Authorisation

EAMW – European Association of Medical Writing

ECs – Ethic Commissions

eCRF – Electronic Case Report Form

EMA – European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

GIST – Gastrointestinal Stromal Tumor

IBS – Irritable Bowel Syndrome

IC – Informed Consent

ICH – International Conference on Harmonization

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

ISF – Investigator Study File

IV - Intravenous

KOL – Key Opinion Leaders

LDA - Limitada

m - million

MAH – Marketing Authorization Holder

MQP&BD – Medical Qualified Person and Business Development

MW – Medical Writing

NCBI – National Center for Biotechnology Information

NIH – National Institute of Health

NLM – National Library of Medicine

NPS – National Pharmacovigilance System

PI – Principal Investigator

PIS – Patient Information Sheet

PhVWP – Pharmacovigilance Working Party

PwC - PricewaterhouseCoopers

QA – Quality Assurance

QMS – Quality Management System

QPPV – Qualified Person for Pharmacovigilance

RA – Regulatory Affairs

R&D – Research and Development

Rx – Prescription for medicine

SACS – *Secção Autónoma das Ciências da Saúde* – Health Sciences Section

SC – Scientific Consulter

SDV – Source Data Verification

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

ST - Statistics

UA – *Universidade de Aveiro*

USD – United States Dollar

WHO – World Health Organization

XML – Extensible Mark-up Language

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1. Introduction

The present work consists on a curricular training report, made effective and conclusive as part of the Master's Degree in Pharmaceutical Biomedicine, SACS, UA.
The curricular training took place in Novexem Portugal, a CRO located in Coimbra, and had duration of 11 months, from September 2010 to July 2011.

This document aims to present the activities developed during my training period in Novexem Portugal, as well as all the learning outcomes and skills acquired during this journey.

In general terms, this report will address the current state of the art in pharmaceutical research area, my vision about the institution where the training period took place, as well as the objectives proposed at the beginning of this period.
After that, there is a description of the developed activities in every training area, a brief discussion of relevant aspects of this period as well as the conclusions that I could collect.

1.1. State of the Art

The global pharmaceutical industry is a multinational industry that is a highly regulated, capital intensive [it is valued at around USDbn880 (United States Dollar) in 2011] (1) and which is driven by large research and development expenditures. The industry is primarily privately owned and is technologically sophisticated (2).

In 2011, pharmaemerging markets are expected to grow 15-17%, while the five major European markets (Germany, France, Italy, Spain and United Kingdom) collectively will grow at a 1-3% pace (3).

Measured by the number of drugs approved per dollar of Research and Development (R&D), the innovative performance of the drug industry appears to have declined (4).
New-drug approvals have remained roughly constant since 1950, while the cost of drug development has soared (4-5).

The costs associated with bringing a drug onto the market have increased at a phenomenal rate in recent years (6). (…) total R&D costs per new drug were around USDm897 in 2003, an increase of 59.32% over 1999, when the figure stood at USDm563. A single failure of a drug would have significant impact in terms of lost opportunity and future prospects of a company(6). Table 1 (7) shows the trends in R&D spending over the recent years.

Table 1 – Global Pharmaceutical R&D Spend Analysis (7)

Global R&D Spend Analysis									
	2002	**2004**	**2006**	**2008**	**2009**	**2010**	**2012**	**2014**	**2016**
Pharma R&D Spend (USDbn)	68.4	86.2	104.9	125.6	124.5	127.4	132.3	139.1	145.5
Growth per year		*11%*	*11%*	*8%*	*-1%*	*2%*	*2%*	*3%*	*2%*
Rx Sales (USDbn)	350	448	530	628	644	662	699	746	785
Growth per year		*11%*	*9%*	*8%*	*3%*	*3%*	*2%*	*3%*	*2%*
R&D as % of Rx Sales	19.6%	19.3%	19.8%	20.0%	19.3%	19.2%	18.9%	18.6%	18.5%
Cumulative R&D spend (02-09)	$798bn								
Annual R&D spend growth (02-08)	10.6%								
Annual R&D spend growth (09-16)	2.3%								

R&D – Research and Development; Rx – Prescription for medicine; USDbn – United States billion dollars

The pharmaceutical sector is undergoing dramatic change, primarily caused by reduced output of new medicines from R&D laboratories, drug pricing pressures, stricter regulatory environments and overall current economic downturn (8).

An important issue for the sector is that it is confronted with rising R&D costs while, at the same time, the success rate of innovation seems to have declined. The rising in R&D costs seems to be mainly the result of two factors: 1) many of the "easy" inventions have already been made, making current clinical development more complex; and 2) regulation (e.g. requirements on clinical development) has become stricter, and differs by country, which makes testing more expensive (9).

In 2009, PricewaterhouseCoopers (PwC) reported that the pharmaceutical industry was investing twice as much as it had been a decade ago in order to produce only 40% of new medicines (10).

PWC also reported that, although the total number of projects in the R&D pipeline has continued to increase in recent years, there is only limited growth in the number of candidate products for Phase III and the success rates of moving from Phase II to III are in decline (9).

Pharmaceutical industry has had an impressive history of blockbuster drugs, life saving medicines and new therapies that have enhanced the lives of many (11). Currently, it is facing challenges that lead to high costs of drug development at extended timelines (11).

Under pressure to reduce drug prices, pharmaceutical industry is intensively searching for efficiencies in their product development process. Meanwhile, the number of new drugs entering clinical testing increased by 52% since 2000 (12). The combination of more drugs in the pipeline and the need to test them more extensively is straining the organizational capacity of companies sponsoring those drugs. As a result, more and more drug companies are outsourcing their clinical research to CRO (12).

The total CRO market size was estimated at USDbn20 in 2008 and is expected to grow at an annual rate of 8.5% to reach USDbn35 by 2015. The market is highly fragmented and the number of CROs worldwide has reached over 1.100, despite continued consolidation (13).

CROs provide substantial global capacity to drug developers and have become a critical contributor to clinical trial activities (13).

Rising costs and falling in the productivity, among other trends, were driving pharmaceutical companies to outsource an increasing range of functions to CROs in search of time and cost savings (13).

The current economical situation has affected major pharmaceutical companies which are addressing existing and new issues within their own organizations. As a result, new operation models are likely going to evolve within both CRO and pharmaceutical industry. Outsourcing service providers and CROs should be prepared to face these changes. On the other hand, pharmaceutical industry will become more careful and pickier when selecting ideal outsourcing service partners in the near future. Major CRO will be preferred since they are well equipped and capable of conducting a wide range of drug R&D and/or manufacturing work. However, to more effectively cost control, small CROs will be selected for being technically capable (14).

1.2. Vision on the institution

Novexem Portugal is a full service CRO founded in 2007. After two years in Cantanhede, in Biocant Park, it moved to centre of Coimbra, where it is currently based. As a CRO, Novexem Portugal provides scientific consulting services in the pharmaceutical area. Its main business areas are clinical development, medical marketing, pharmacovigilance and regulatory affairs, pharmacoeconomics, and outsourcing. Regarding clinical development, Novexem's major activities are R&D, clinical trials, epidemiology and late phase research, and biostatistics. Although Novexem Portugal is run independently, it shares some resources with Salutis Research, which is a Spanish CRO. In order to enhance the promotion of both companies beyond the Iberian Pharmaceutical Market, a branding by the name of Salutis International was created. This branding allows the divulgation and offer of services at an international level, which would be more difficult individually.

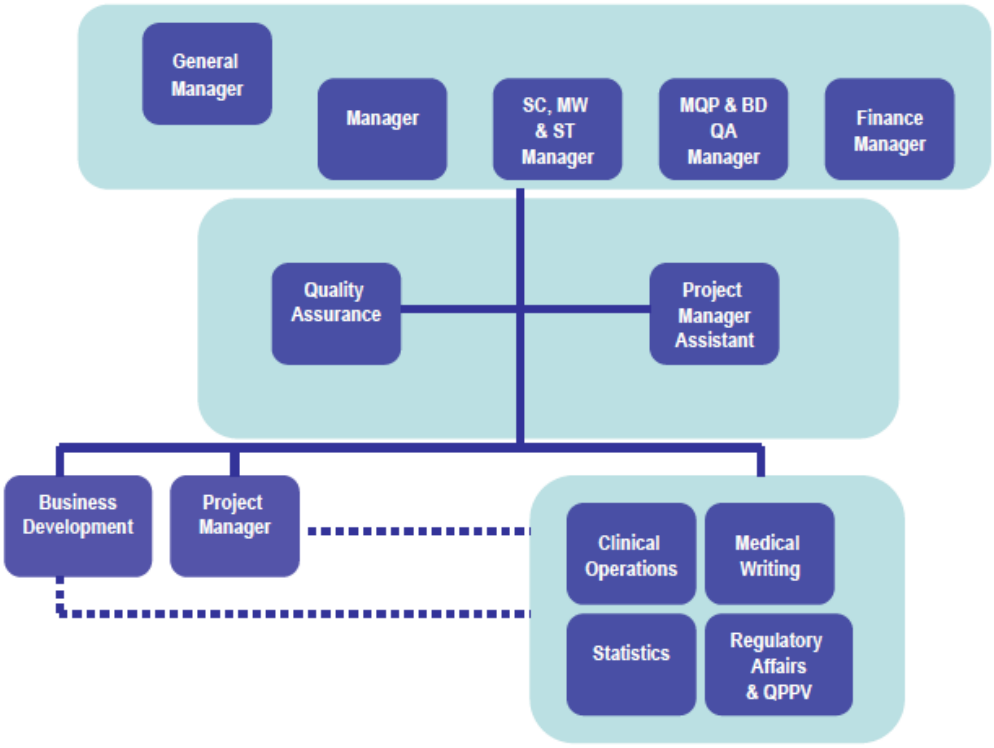

Figure 1 – Novexem's Organizational Chart

SC- Scientific Consulter; MW- Medical Writing; ST- Statistics; MQP&BD- Medical Qualified Person and Business Development; QA- Quality Assurance; QPPV- Qualified Person for Pharmacovigilance;

Source: Novexem Portugal

1.2.1. Human Resources

The professional body of Novexem Portugal is formed by a total of 11 elements. Teresa Almeida, PhD and with a Master's Degree in Cellular Biology (Neurosciences), is the General Manager of Novexem Portugal. The other elements are:

- Alexandra Moura, secretarial training, exerting functions as Administrative Assistant;
- Ana Raquel Queijo, pharmacist, exerting functions as Project Manager;
- Ana Vanessa Mendes, pharmacist, exerting functions as Lead Clinical Research Associate (CRA);
- Jaime Colaço, biochemical, exerting functions as Commercial (Business Development);
- Marisa Serra, accountant, exerting function as financial responsible;
- Olga Calado, pharmacist, exerting functions in Pharmacovigilance and Quality Department;
- Patrícia Barreto, pharmacist, exerting functions as Medical Writer, Project Leader and Lead CRA;
- Pedro Mota Veiga, statistician, exerting functions as Project Manager and Statistician;
- Rute Figueiredo, nurse, exerting functions in Call-Center;
- Sandra Poiarez, anthropologist, exerting functions as Project Assistant;

1.3. Training Objectives

Primary Objectives:

- To bring me closer to the reality of working in pharmaceutical research;
- To apply and train the tools acquired during the Master's course;
- To obtain specific working tools and techniques for developing activities in pharmaceutical research area;
- To identify particular areas of interest within pharmaceutical research;
- To establish a working contacts network;

Secondary Objectives:

- To identify the organizational structure of Novexem Portugal;
- To identify areas of activity of the company and their processes;

- To get acquainted with the general framework of Quality Management System (QMS) in Novexem Portugal and its supporting documentation;
- To submit different documents to the various authorities;
- To identify the Pharmacovigilance System structure;
- To identify and participate in Pharmacovigilance activities applied to projects (eg. AE management and notification);
- To read and review clinical trials' protocols;
- To submit clinical trials or studies to the various entities (Health Authorities, ECs, investigators, centres, hospital services,…);
- To perform Feasibility activities;
- To conduct pre-study and initiation visits;
- To conduct monitoring visits;
- To resolve Queries;
- To conduct study close-out visits;
- To manage clinical trials medication;
- To participate in project meetings;
- To perform bibliographic research;
- To elaborate and submit articles;
- To develop and submit abstracts and posters;
- To develop Case Report Form (CRF) and Informed Consent (IC);
- To translate articles;
- To elaborate Consensus and Clinical Practice Guidelines;

2. On-the-Job Training

2.1. Quality Assurance

Novexem Portugal is currently in the process of accreditation by NP EN ISO 9001:2008 (15).
The ISO 9000 family of standards represents **an international consensus on good quality management practices**. It consists of standards and guidelines relating to QMSs and related supporting standards.
ISO 9001:2008 is the standard that provides **a set of standardized requirements for a QMS**, regardless of what the user organization does, its size, or whether it is in the private, or public sector. It is the only standard in the family against which organizations can be certified – although **certification is not a compulsory requirement** of the standard (15).
Regarding QMS, it generally requires:

- Determination of processes, sequence and interactions;
- Criteria to ensure operation and control;
- Availability of resources;
- Monitoring, measurement and analysis of processes;
- Implementation of actions to achieve results.

In relation to documentation, QMS asks for:

- Quality Manual
- Documents Control
- Registries Control

In Novexem, four main processes can be identified – Planning and Management Process, Commercial Process, Production Process and Measurement and Analysis Process. As it is seen in figure 2, these processes are not static; they communicate and interact between them.

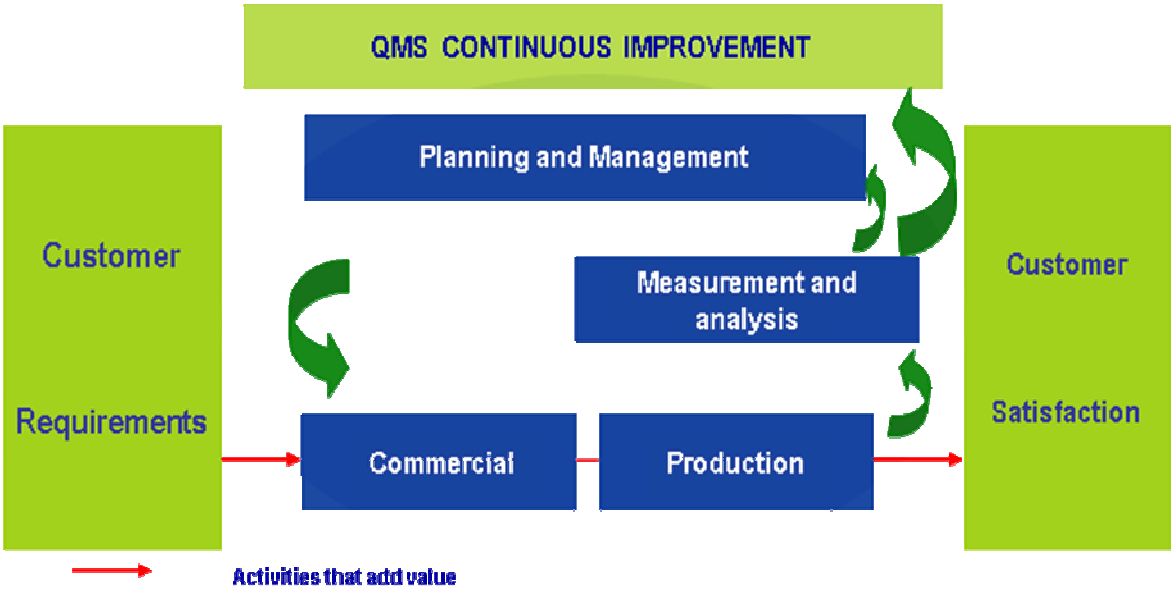

Figure 2 – Novexem's Quality Management System Model

QMS – Quality Management System

Source: Novexem Portugal

The processes are a crucial tool for converting customers' requirements and ideas into tangible outcomes that try to satisfy their expectations, as well as to improve QMS.

The procedures define how activities are performed and processes activated. In the case of Novexem they are:

- General Company organization
- Epidemiologic studies
- Observational studies
- Clinical Study Management
- Project Managements
- Human Resources
- Clinical Trials
- Medical Writing
- Pharmacovigilance
- Statistics

Novexem Portugal looks for a competitive differentiation guarantee results that will allow internal development and stability in the market.

Regarding this section - Quality Assurance- no practice activity was developed. The inputs in this area resulted from internal training.

2.2. Pharmacovigilance and Regulatory Affairs

2.2.1. Pharmacovigilance

According to World Health Organization (WHO), Pharmacovigilance is defined as “the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health” (16).

Pharmacovigilance is conducted by pharmaceutical industries on their products, by regulatory authorities in every product and by healthcare providers by reporting AEs to the Authorities or Pharmaceutical Industry.

Pharmacovigilance legislation is reflected on Decree-Law 176/2006 of August 30th (17) and Law 46/2004 of August 19th (18) in Portugal, and on Directive 2001/83/EC (19), Directive 2001/20/EC (20) and Regulation (EC) Nº 726/2004 (21) in Europe.

In December 2010, a new Pharmacovigilance legislation (Regulation (EU) No 1235/2010 (22) and Directive 2010/84/EU (23)) was adopted by the European Parliament and European Council.

The legislation is effective from July 2012 and it will mainly impact Marketing authorisation applicants and holders. The legislation aims to make roles and responsibilities clear, minimise duplication of effort, free up resources by rationalising and simplifying adverse drug reaction reporting and periodic safety update report and establish a clear legal framework for post-authorisation monitoring (24).

The main regulatory entities that coordinate Pharmacovigilance area are:

- **EMA – European Medicines Agency**

  The Pharmacovigilance system in the European Union (EU) operates with the management and involvement of national competent authorities, the European Commission as the competent authority for medicinal products authorised centrally for the whole EU and the EMA.

  Within this system, it is the role of EMA to co-ordinate the EU Pharmacovigilance system and to ensure the provision of advice for the safe and effective use of medicines.

- **CHMP – Committee for Medicinal Products for Human Use**

  The CHMP is one of the committees created by EMA. It is responsible for preparing the agency's opinions on all questions concerning medicines for human use (25). It also adopts guidelines provided by International Conference on Harmonization (ICH).

  Subsequent monitoring of the safety of authorised medicines is conducted through the EU's network of national medicines agencies, in close cooperation with healthcare professionals and the pharmaceutical companies themselves. The CHMP plays an important role in this EU-wide 'pharmacovigilance' activity by closely monitoring reports of potential safety concerns and, when necessary, making recommendations to the European Commission regarding changes to a medicine's marketing authorisation, or its suspension/withdrawal from the market (26).

  The CHMP establishes a number of working parties at the beginning of each three-year mandate. These working parties have expertise in a particular scientific field, and are composed of members selected from the European experts list maintained by the Agency (25).
  The Pharmacovigilance Working Party (PhVWP) provides recommendations to the CHMP on all matters relating directly or indirectly to pharmacovigilance, the constant monitoring of medicinal products on the market (25).

- **ICH**

  ICH is a joint initiative between Industry and Authorities as partners in discussion, to ensure safety, quality and efficacy of drugs.
  ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for

pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.

Launched in 1990, ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States.

Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include:

- preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness;
- streamlining the regulatory assessment process for new drug applications; and
- reducing the development times and resources for drug development.

Harmonisation is achieved through the development of ICH Tripartite Guidelines. The Guidelines are developed through a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines (27).

- **INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P in Portugal and authorities of other member states**

INFARMED is the entity responsible for the monitoring, coordination and implementation of the Portuguese National Pharmacovigilance System (NPS).

Portuguese NPS was created in order to define responsibilities and procedures relating to national Pharmacovigilance activities. It is described on Decree-Law 176/2006.

NPS is coordinated, monitored and regulated by the Directorate of Medicines Risk Management with the collaboration of its NPS Management Unit. NPS if formed by:

- Directorate of Medicines Risk Management
    - Pharmacovigilance Units
        - North Pharmacovigilance Unit
        - Centre Pharmacovigilance Unit
        - Lisboa e Vale do Tejo Pharmacovigilance Unit
        - South Pharmacovigilance Unit
- Health Services
    - Healthcare providers

- Pharmacovigilance Delegates

- Marketing Authorization Holder (MAH) and subcontractors companies for Pharmacovigilance tasks

- **Associations, Committees and Joint Groups**

- **CIOMS – Council for International Organizations of Medical Sciences**

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.

The main objectives of CIOMS are:

· To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;

· To maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO;

· To serve the scientific interests of the international biomedical community in general.

It has developed a series of Pharmacovigilance guidelines, drawn up by a committee of volunteers from industry, regulatory authorities, WHO and others. The main guidelines concern the international reporting form (CIOMS I); periodic safety update reports (CIOMS II); core data sheets (CIOMS III); benefit-risk assessments (CIOMS IV); practical issues in pharmacovigilance (CIOMS V); clinical trial safety data (CIOMS VI); development safety update reports (CIOMS VII); application of signal detection in pharmacovigilance (CIOMS VIII); and practical considerations for development and application of a toolkit for medical product risk management (CIOMS IX) (28).

During the curricular training, the main Pharmacovigilance activities developed were:

- **Internal training on Pharmacovigilance procedures**

  Internal training on pharmaceutical procedures could be decomposed into two main areas:

  1) Self-reading of Novexem's Pharmacovigilance Standard Operating Procedures (SOPs);

  2) Direct training by exhibition and explanation of Pharmacovigilance materials by Novexem's Head of Pharmacovigilance.

- **Pharmacovigilance tasks associated with Patients' Hotline Program**

  This program consists of a hotline for patients taking a specific drug indicated for the treatment of osteoporosis. Patients call the hotline in order to ask for material (needles) for drug administration, when they have doubts on the drug and when they wish to report adverse events (AEs) that they believe are drug-related.
  The Pharmacovigilance SOP demands that, when an AE is reported, data should be collected according to sponsor's requirements, in this case in a template for reporting AEs. After all parameters are full-filled, the document should be sent to the sponsor and receipt-proof fax archived.
  These are the Novexem's Pharmacovigilance responsibilities as agreed in contract. However, if Novexem was fully responsible for Pharmacovigilance activities in this program, other functions would be necessary, for example INFARMED notification when applied.
  For me, this activity as back-up person for collection of adverse reactions was very important as it allowed the implementation of the knowledge acquired on internal training. It was also important as a sample for future pharmacovigilance activities to be developed.

2.2.2. Regulatory Affairs

Regulatory affairs (RA) are the mechanisms by which a business deals with governmental controls and requirements specific to that business. The purpose of regulation is to protect the public in terms of restraining potentially incompetent or irresponsible industrial or commercial activities (29).

RA are a vital part of any pharmaceutical company. RA department acts as liaisons between their company and health authorities such as EMA, FDA and national authorities. RA employees act as a link between regulatory bodies and the company (30).

Among the activities that a CRO has to offer, RA are particularly important for the submission process of different studies in biomedical area to the regulatory authorities.

As summarized by do Vale in “Estudos Observacionais”, there are several types of studies in biomedical research area (31):

- Preclinical studies – laboratory studies that may involve animals or humans, tend to be relatively small and require high accuracy by the researcher;
- Clinical studies – they require active intervention to be made to the subject of research (eg testing a new drug, device or treatment technique) and that the researcher uses randomization;
- Observational or Epidemiological studies – do not involve active intervention, include only observation, for example to evaluate a potential risk; They can also be subdivided according to the criteria of causality:
    - Experimental Epidemiological studies – the investigator controls the exposure and uses randomization as method;
    - Pseudo-experimental studies – controls exposure, but does not use randomization;
    - Non-experimental or observational studies – exposure occurs without the participation of investigators and according to variables that are beyond their control;

In Portugal, conducting clinical trials with drugs for human use is regulated by the juridical regimen established by law nº 46/2004, August 19th (18), transposing into national law the Directive 2001/20/EC of the European Parliament and the Council of April 4th (20) and Eudralex Vol. 10. According to this law, a clinical trial is defined as “any investigation in human subjects intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more experimental drugs, or identify any adverse reactions to one or more medicinal products, or to study absorption, distribution, metabolism and excretion of one or more medicinal products, to ascertain its safety or efficacy” (18, 20).

In order to conduct a clinical trial in Portugal, the sponsor has to submit the clinical trial authorisation (CTA) application form to INFARMED. The authorization conceded by INFARMED just allows the implementation of clinical trials in Portugal.

Before submitting the CTA application form to INFARMED, the sponsor must obtain an EudraCT number. EudraCT is the EU's electronic database of clinical trials. It contains information submitted by sponsors and informs users about ongoing clinical trials in all EU member states and European economic area countries, enabling an overview of multi-state trials. The system also alerts regulatory authorities in Member states in the case of early interruption or termination of a trial (32).

The EudraCT number will be unique to each trial, identifying clinical trials in Portugal or in other member states.

The CTA application form should be submitted written in Portuguese (as well as the proof of fee payment). For all other documents, English language is acceptable. The submission should be in mixed format (paper and CD-ROM):

In paper:

- CTA application form
- EudraCT Confirmation Document
- Fee Payment Proof
- Signed form of application for CTA
- Checklist

In CD-ROM:

- Protocol and Amendments
- Investigator's Brochure
- Extensible Mark-up Language (XML) file – it is the only way of saving a permanent electronic version of the CTA application
- Summary of Product Characteristics (SmPC)
- Remaining checklist elements

Furthermore, the sponsor should also provide INFARMED with the list of other competent authorities to whom the applications were already submitted, the decision data and copies of ECs' opinions.

The conduction of a clinical trial is also necessarily preceded by positive opinion of the appointed EC – Comissão de Ética para a Investigação Clínica (CEIC). The authorization request can be presented simultaneously or not to the aforementioned entities.

CEIC is, according to Law nº 46/2004, an independent body consisting of individuals linked to health and other areas of activity, whose mission is to ensure protection of the rights, safety and welfare of participants in clinical trials, through an opinion on research protocols that are submitted. CEIC assesses the relevance and design of the research protocol, the benefit-risk profile of the proposed intervention, the suitability of the research team, the human resources and materials available in research centres, the provisions on compensation for damages, insurances, the amounts and procedures for compensation of researchers and participants, the recruitment methods, the autonomy of volunteers and also the accessibility and circuit of the experimental drug (33).
The sponsor of the clinical trial has also to ask for authorization of *Comissão Nacional de Protecção de Dados* – National Commission for Data Protection (CNPD) as well as of authorization of all boards of directors of involved hospitals.

CNPD is an independent administrative body. Its generic allocation is to control and supervise the processing of personal data in strict respect for human rights and fundamental freedoms and guarantees enshrined in the portuguese Constitution and Law (34).

According to the Directive 2001/20/EC, a non-interventional trial is defined as: "*a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advanced by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data*".
This kind of studies is excluded from the scope of this Directive. The purpose for excluding these trials from the scope of the Directive 2001/20/EC is that these trials are typically of a lower risk than interventional clinical trials.

Currently, there are still no specific guidelines and/or legislation that coordinate the implementation of observational studies. The main requirements that the sponsor must complete before study initiation are obtaining authorization for study implementation by CNPD and the authorizations of all boards of directors of involved hospitals. Although this lack exists, it is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for

Pharmacoepidemiology (35). In some of the ICH regions, local laws and guidelines also apply to the design and conduction of observational studies and should be followed (36).

The developed activities regarding RA, are described below in Clinical Operations section.

2.3. Clinical Operations

Clinical Operations is where medical monitoring, product safety, clinical monitoring, and project management come together to provide clinical trial management.

The developed activities refer to different steps in the conduction of a project, and try to reflect the reality of what was developed for each study.

- **Reading and Reviewing clinical trials protocols**

  Being familiar with different study protocols is essential for the development and participation in activities related to the studies. Depending on the tasks to perform, more or less details are needed. During the training period in Novexem Portugal, before any intervention or activities carried out for a study, the protocol was always previously read and critically examined.
  This allowed me to establish a logical and coherent thinking during required tasks and also not to fail in the premise of the study and its critical steps.

- **Submission of clinical trials or studies to the authorities (Health Authorities, CEICs, investigators, centres, hospital services)**

  - **Observational study regarding the use antifungal therapy in haemato-oncology patients**

    The main activity related with the submission of studies to regulatory authorities was a prospective, multicentre, observational study regarding the use of empiric and pre-emptive antifungal therapy in haemato-oncology patients with neutropenia to CNPD.
    As clinical studies deal every single day with huge amount of data relating to participants in studies, CNPD controls and ensures that there is no abuse and/or misuse of this information.

For this activity, it was necessary to fill in CNPD submission form according to the information about the study. Among other information, the purpose of processing personal data, data contained in each record, method of collection, communication and security details were asked. Along with the submission form, other required documents and fee payment were sent. After this process, and before the start of the study, a positive opinion of CNPD has to be awaited.

This activity was very useful for future submissions as the process is basically always the same, differing on the data to be submitted.

Submission to CNPD is a process which, although not complicated, is not intuitive as some requested fields are not very clear and comprehensive.

- **Performing pre-study visit and study initiation visit**

A pre-study visit takes place after a potential Principal Investigator (PI) indicates interest in a specific clinical trial. The purpose of this visit is to determine the site ability to conduct the study. Pre-study visit is meant simply to assess the feasibility of conducting the study and to determine whether the site can manage protocol-specific requirements (37).

Once the PI agrees to participate in the study and signs the contract with the sponsor, the protocol and consent form are approved and clinical supplies are shipped to the site, a study initiation visit may finally be conducted. This visit verifies that the investigator and other site study personnel understand the investigators' obligations, the protocol and the investigational product being studied (37).

  - **Observational Transplantation Study**

The first study initiation visit conducted during the training period was a visit as part of an observational study regarding kidney transplantation. During this visit, all investigators were present. They were already familiar with the study protocol and the required procedures; however, they all raised questions that were promptly answered. They were explained and made a live demonstration on how to work with the electronic platform of the CRF in order to learn how to submit the data. Investigators were provided with an Investigator Study File (ISF) for each one and the investigators' declaration of acceptance were

collected. It was very interesting to observe this first visit to understand how it is usually conducted and the topics that are addressed.

- **Haemato-Oncology Study** In this visit, and similarly to the study mentioned above, investigators were already familiar with study protocol. The session intended to make a live demonstration on how to submit data on the electronic case report form (eCRF).

  These activities help to understand how a study initiation visit is conducted and what are the main topics discussed.

- **Conducting monitoring visit**

  - **Study evaluating Chemotherapy and/or Hormone Therapy With or Without a biphosphonate in Treating Women with Stage II or Stage III Breast Cancer**

    According to ICH E6 – Guideline for Good Clinical Practice – monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirements (38).

    After one or more subjects are enrolled in the study, a monitoring visit may be scheduled to evaluate how the study is being conducted and to perform source data verification (SDV). There may be numerous periodic monitoring visits conducted at each site throughout the trial (37).

    Monitoring visits have being performed in a clinical trial intended to evaluate if an adjuvant biphosphonate reduces or not recurrence in patients with high-risk localized breast cancer.

    Monitoring visits start being prepared at the office, weeks before the scheduled date. It is very important to take stock of the status of all pending issues, make a plan of the visit and send to all stakeholders, ask for all materials that will be necessary (e.g patients' clinical records) and for authorizations to visit other departments like pharmacy.

Once in the centre, the developed visit plan is met. In this case, different activities were performed: CRFs were compared with patients' clinical record and then monitored and collected, pharmacy records were monitored, and pending issues were solved and archived.

After the visit, it is necessary to do some office work. All collected data have to be copied and archived; pending issues status have to be updated; study forms regarding different aspects of the visit have to be completed. The visit ends with the submission of a monitoring visit report to the sponsor and a follow-up letter to the PI.

Although different clinical trials have different monitoring requirements, it allowed me to know and understand the different activities underlying a monitoring visit and also to implement some of the knowledge acquired on classes.

- **Queries resolution**

Queries are questionable data that must be explained. If any discrepancies or inconsistencies which need to be corrected as per the study protocol are found in clinical data, a query is raised to the site and should be clarified by the Data Manager (39).
During the training period, just in one situation was it possible to receive a query. It was an incongruence in filling one CRF form. The Data Manager was notified and promptly requested the PI to change the form.

- **Study close-out visit**

The final visit is performed after the last patient in the study completes the last follow-up visit. In this visit, the monitor retrieves all remaining CRFs, and completes all device inventories. In the close-out visit the monitor should achieve the following (40):

- To finalize drug accountability inventory to ensure that all drugs used in the study are accounted for;
- To verify that all patients CRF are completed and all copies are retrieved from the site.
- To close all open items from previous monitoring visits;

- To complete the site regulatory file review;
- To ensure that all AEs are documented and reported appropriately;
- To confirm that the PI has notified the study participants, ECs and, if required, regulatory authorities that the study has been completed (when applicable- the sponsor can perform these activities);

o **Phase III, multicentre, randomized, open-label trial of neoadjuvant chemotherapy versus the same chemotherapy plus Trastuzumab in women with locally advanced HER2-positive breast cancer**

The only study close-out visit conducted during the training period was in relation to a clinical trial intended to evaluate the role of Trastuzumab as neoadjuvant chemotherapy in patients with locally advanced HER2-positive breast cancer.
In this visit, it was very important to solve all pending issues that were ongoing from previous monitoring visits as well as to answer the incongruence found on trial documentation. Medication had already been collected and accounted for in all previous visits, so there was no need to deal with this topic this time.
Pending documentation was completed, copied and archived and ultimate reconciliation of documentation was performed. Centre's study files were closed. A close-out visit report was prepared as well as a follow-up letter for PI.

- **Project Support Activities**

Project Support Activities represent different sub-tasks that give assistance for the conduction of the related projects.

o **Observational Study regarding the evaluation of microalbuminuria levels in Portuguese patients.**

This observational study involved 500 investigators from all over the country and intended to evaluate microalbuminuria prevalence in four main groups: Non-diabetic normotensive patients, diabetic patients, hypertensive patients and also diabetic and hypertensive patients. As a secondary objective, it was also intended to assess the geographic distribution of the data.

- **Logistic tasks**

This study involved sending laptops to each investigator in order to proceed with data entry in the electronic CRF. The computers were coded and sent to investigators' meeting reunion. Along with the laptop, a mobile internet device and microalbuminuria test strips were also sent. The shipments were traced and documents associating each investigator with the code of the submitted material were created. Separately, the researchers were sent letters describing the user name and password to access the eCRF.

- **Quality control**

In order to assess the quality of data entered in the eCRF, a brief questionnaire was prepared and approved by the sponsor. Investigators were asked to answer the questions in a phone-call.
After the questionnaire, data were statistically analyzed.

o **Support Program for patients with osteoporosis**

This project intended to implement a telephonic hotline for the support of patients/caregivers with osteoporosis.
By calling this hotline, patients/caregivers could:

- Sign in/ Validate the enrolment in the program ;
- Schedule home visits;
- Clarify some doubts about the product (according to the SmPC) and administration, program operation, communication of AEs and claims of product quality.

The developed tasks on the scope of this project have greatly varied. I was requested to occasionally replace the team member responsible for the call-center. As a back-up, it was necessary to pick-up all phone calls, answer all raised questions, and deal with all procedures associated. These procedures included:

- The management of AEs, i.e., collecting the maximum information available from the patient, filling in the AE form and sending it back to the sponsor;

- Home visits scheduling: Novexem provides a team of nurses that go to the patients' house in order to clarify questions regarding the administration of the drug and demonstrate how this is done.

- Needles request management. As this drug is administered via Intravenous (IV), patients undergoing this therapy need needles for successfully completing treatment. Novexem is responsible for receiving needles request form and send needles for drug administration to patients on the program. Novexem also sends patients needles request form every month, so they can ask, this frequently, for needles.

- Novexem also sends ICs to the patients so they can allow their participation in this program. It is also necessary to manage and account for all program materials: needles, envelops, ICs, needles requesting form, travel bags and materials required for home visits.

o **Project for assessment of clinical practitioners' opinion regarding the use of haemostatic and sealant drugs.**

This project intended to ascertain what the opinion of clinical practitioners and pharmacists was, regarding the use of haemostatic and sealant drugs. It was proposed to the sponsor to conduct a questionnaire, in order to obtain conclusions about the current clinical practices in this field.

Questionnaires were conducted personally and via phone call and were intended to different heads of service. We approached the heads of cardiovascular surgery, cardiothoracic surgery, urologic surgery, general surgery and pharmaceutical services of hospitals pointed by the sponsor.

Questionnaires contained several information fields, such as the number and types of surgeries performed per year, the haemostatic/ sealant products used and the reasons for their use, and classification of the different products regarding their efficacy, safety, tolerability, commodity and cost-benefit relationship. In the case of the directors of pharmaceutical services, questions were a little bit different, focusing on pharmacy stock numbers, circuit till surgery and storage advantages.

Results of the questionnaires were analyzed by Novexem´s statistical department and a final report was prepared.

This task revealed itself very challenging as the contact with clinical practitioners was not always easy. It was very difficult to directly talk and convince them to participate in the project.

- **Other projects**

During this training period, several other activities were performed for the support of projects. They are referred in this section, as they were small tasks, or because they were performed on an occasional manner.

- The first activity described is the quality control of an eCRF for the haemato-oncology study. When the eCRF is completed, before sending it to the customer, it has to be internally tested and assessed to prove that all the requirements were met in order to satisfy the customer and the protocol.

- Other activity occasionally performed was the development of monthly reports regarding transplantation studies. In these studies, Novexem is also responsible for the management of the eCRF. At the end of every month, Novexem has to analyze all data submitted by investigators. These reports allow the sponsor to track recruitment rates in every centre, as well as to see if all parameters are being met or if there have been protocol deviations.

- Another project that Novexem is currently managing is a support project for patients with erectile dysfunction. Elements of Novexem nursing and psychology teams are in different pharmacies, clarifying patients and collecting answers for a questionnaire regarding their pathology and life-style. These questionnaires are then collected and sent to Novexem where they are submitted to a quality control, to understand if data is valid and is correctly filled in.

- Finally, another activity that was included in this section was a project that intended to collect the opinion of practitioners in the field of neurology regarding multiple sclerosis. A questionnaire was prepared and approved by the sponsor and then the heads of neurology of selected hospitals were contacted by telephone in order to answer these questions. Once again, this kind of approach was very difficult to implement as the availability and receptivity was not always achieved.

2.4. Medical Writing

“Medical Writing is about communicating clinical and scientific data and information to a range of audiences in a wide variety of different formats.”(41), this is the definition given by the European Association of Medical Writing (EAMW).

There are several professional organizations around the world that fight for the interests of medical writing professionals. Among them are the American Medical Writers Association (42), Australasian Medical Writers Association (43), EAMW (44) and Indian Medical Writers Association (45). These organizations allow medical writers to meet and share knowledge and experience. They promote professional development and standards of documentation excellence, and help writers find career opportunities.

Medical Writing was the field in which more activities were developed during the training period. It included the generation of review articles, scientific posters, translations, elaboration of CRFs, references management, among others in detail below. It demanded a relative domain of English and Spanish languages, as well as knowledge of scientific writing skills.

Medical Writing activities were much diversified and helped me to greatly develop my knowledge on this area and to be ready for the requirements of a career as medical writer.

- **CRF (Case Report Form) structure definition**

  CRFs are questionnaires or instruments that are used to collect required data about cases or subjects enrolled in a study in a structured and standardized manner to facilitate reliable, consistent and clean data for analysis. General purposes of the CRF are to: meet the objectives of research; obtain most complete and accurate information possible and do this within the limits of available time and resources (46).

  The definition of CRF structure was first performed in the context of a project for an observational study for multiple sclerosis. It was supposed, based on the specifications of the study protocol and its variables, to create the main structure and to establish the correlations between variables for further graphic and informatics development.

  This kind of activity was then repeated for another observational study in the context of patients with hypertension. The same assumptions were taken into account for the development of this CRF.

  It was very interesting to be involved in this task because it requires a deep knowledge of the study protocol in order to understand the different correlations between variables so the CRF can reflect that. Different scenarios had to be thought so when data is entered, it is the most correct and concise one and to make the analyses easier.

- **Development of slide-kit**

  Slide-kits are a convenient way to provide clients, customers, and colleagues detailed information about a product. The developed slide-kit was subordinated to a specific antispasmodic. This document was in a power point format and pretended to present the main characteristics of the product. It contemplated the mechanism of action in pathophysiologic cases, safety and efficacy information, the approved therapeutic indications and scientific results of studies comparing the brand name with its direct competitors.

  The main objective was to situate the product in the market and to highlight the advantages that it presented.

  This activity was more oriented to the marketing field, an area in which my experience was not very significant so it was very interesting and fruitful to be able to develop my skills in this area.

- **Article References Management**

  References management is the activity responsible for assuring that all sources in the text are well cited, that references are presented according to journal's requirements for publication and that appropriate reference management tools are being used.

  This task was asked to be performed in the ambit of an article regarding Spanish severity scales for the assessment of *acne vulgaris*.

  This activity required domain of tools such as EndNote® and PubMED. EndNote® is a reference management software and PubMED is "a free resource that is developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH). PubMed comprises over 20 million citations for biomedical literature from MEDLINE, life science journals, and online books."(47). This activity was very useful as it allowed the improvement of researching skills, as well as the use of reference management tools. It is of special importance because both skills are transversally used across every single developed article.

- **Development of Articles**

  - **Pathology Review**

    A review article is expected to provide a summary and/or a synthesis of the findings of selected research contributions being published by other authors. The main purpose of a review article is to examine the current state of the

relevant publications on a given topic and to initiate a discussion about the research methodologies and the findings related to the said topic (48).

The requested task was to delineate an article that would review a specific pathology – Gastrointestinal Stromal Tumor (GIST) – and the use of a tyrosine kinase inhibitor as a treatment option. In order to complete this objective, Salutis medical-writing department provided the most clinically relevant articles subordinated to the theme and the statistical results of a collection of clinical cases reported by Spanish general practitioners. In Portugal, these data were analyzed and structured on the review article. Results were discussed and conclusions were obtained. Afterwards, the article was sent to Spain for final revision.

This activity required a full knowledge of the different sections of a review article. In addition, the ability to critically read and interpret the results, as well as obtaining coherent results was of extreme importance. In this kind of activities, dedication has to be complete and knowledge integration is very important.

- **Clinical Cases Compilation**

This type of article is a very particular situation because, unlike other articles, it does not follow such a hard structure. On a clinical cases compilation there are still an abstract and an introduction that usually present the background on the specific topic. The methods section is usually the same, as it explains how data was obtained and managed. The Results and Discussion/Conclusions sections tend to differ, as in the case of clinical cases compilation these sections usually describe the results separately, by clinical case, and the conclusions may be presented in general or in particular.

This task had origin on an initiative of a pharmaceutical company, which supported the publication of a little book in Spanish with the most interesting cases of GIST in Spain. From all these cases, the 5 best ones were selected and used for the compilation article.

This activity was very interesting as it made possible to deal with a different and particular type of article, not used very often.

- **Consensus Decision-Making Articles**

More than focusing on presenting results, a consensus decision-making article intends to present the conclusions that emerged from discussion on a specific subject between experts, Key Opinion Leaders (KOL) and other relevant elements in that field.

In this case, the requested article was supposed to be divided into 2 different sections. The first section should have presented the scientific evidence available on the use of a specific antispasmodic in the treatment of Irritable Bowel Syndrome (IBS). On the other hand, the second section was supposed to present the results of a survey where general practitioners answered about the disease, diagnosis and treatment options.

This is still an ongoing task as the results of the survey are still being collected. They will be collected in 3 rounds on Spanish general practitioners and, after the 3rd round, all the compiled results will be inserted on the already advanced article.

- **Translations**

Another activity that is relatively frequent on Medical Writing is the translation of different documents. In most of the cases translations are from Spanish (Castilian) to English but also from Portuguese to Spanish. Translating articles is not always as straightforward as might be thought. Sometimes it can be very challenging, mainly in scientific areas, because of technical terms that are used and that require much research. It is also an area that requires constant focus during the task because the smallest error can adulterate the meaning of the text and compromise the validity of the data presented.

- **Clinical Practice Guidance on Haemathology**

This document was a clinical practice guideline for the first line treatment of patients with a specific type of lymphoma after relapse. It was created by a group of Spanish doctors by discussing the available scientific evidence. The article was in Spanish and had to be translated into English for further submission to an international journal.

- **Cases on Breast Cancer**

This document is a clinical-case review that was intended to describe the clinical experience in patients with breast cancer and the use of Aromatase Inhibitors (AI) as adjuvant treatment. The original document was also in Spanish and was then translated into English. Beyond the translation, it was necessary to search for the chosen journal's submission criteria and adaptation of the necessary fields.

- **Proposals for the commercial area**

  The activities of medical writing team are not limited to scientific and technical writing. Novexem Portugal provides services both nationally and internationally and, thus, it is natural that the requested proposals are sent in the language of the client or, when not possible, in English. In the case of the developed activity, a proposal created by Commercial Area of Novexem Portugal in Portuguese, for a company in Spain, was translated into Spanish (Castilian).

- **Creation of Concept Sheet**

Clinical trial concept sheets are short summary plans for testing a new drug, a brief summary of the research design and implementation. It generally contains sections such as objectives, eligibility criteria, study design, treatment plan, treatment modifications, definitions of study endpoints and a definition of patient evaluability (49). Aside from helping to structure the final study protocol, the concept sheet can be used to communicate basic scientific aspects of the trial and gather feedback (50).
This document was developed in the context of an observational study for assessing safety and effectiveness of the sponsor's product for the treatment of hypertension.
This task was made easier by the fact that the company had previously provided the protocol of a similar study. Thus, it was relatively easy to transpose it for this study and fill in all the requested information fields.

- **Creation of Informed Consent and Patient Information Sheet**

A proper IC is essential. Partly as a result of terrible things done in name of clinical research, various entities developed guidelines, such as the Nuremberg Code, the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (51). Carrying out research on persons without their knowledge or permission violates their autonomy, liberty and dignity. IC also helps to protect participants because they may decline to participate in research whose risks they consider unacceptable (52). It has several components, as reviewed by Derenzo and Moss in "Writing Clinical Protocols – Ethical Considerations" (53):

  - A statement that the study involves research, an explanation of the purposes of the research, the anticipated duration of the subject's participation, and a description of the procedures to be followed, identifying those procedures that are experimental;

  - A description of reasonably foreseeable risks or discomforts and benefits to the subject;

- A description of appropriate alternative procedures or courses of treatment, if any, that may be advantageous for the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- For research involving more than minimal risk, an explanation of whether there will be any compensation and/or medical treatment provided in the event of a research-related injury or illness, and if so, what it is or where further information can be obtained;
- The name(s) and contact information of persons to whom questions should be addressed about the research, the rights of research subjects, and research-related injuries;
- A statement that participation in research is voluntary and that refusal to participate in the study or discontinuation of study participation after enrolment will not engender/result in penalty or loss of benefits to which the prospective or participating subject would otherwise have been entitled.

Every trial must also provide an information sheet that is primarily developed for patients and their carers (54). The patient information sheet (PIS) outlines the information that a patient should need to be able to make an informed decision about whether they want to participate in a trial (54). According to Kerr *et al* in "Clinical Trials Explained – A Guide to Clinical Trials in the NHS for Healthcare Professionals", the main features of a patient information sheet include (54):

- A summary of the clinical trial protocol in language that is clear and concise and easy to understand;
- A list of the characteristics that the clinical trial team need the patients to meet in order to participate;
- A statement of the known and potential benefits and risks to patients; and
- An outline of what will be expected of a participant.

Developing the IC and PIS was related with the already described observational study on patients with hypertension. This activity allowed direct contact with the structure of an IC and PIS. It was necessary to clearly understand their structure and then make some adjustments and adaptations according to available protocol information.

- **Re-structure of articles**

    - **Article regarding a haemostatic/sealant product**

      This task consisted on making modifications on a draft paper regarding the use of a haemostatic/sealant product on vascular surgery. It was supposed to modify the different sections of the draft in order to comply with all supposed requirements of an article. It was also necessary to re-run the search criteria on Medline in order to refresh the available sources of data to present updated and reliable results.

    - **Clinical endoscopic and histology for abdominal pain**

      In this case, it was supposed to adapt an original document into a scientific article. The document was a Master's Degree thesis entitled "Clinical, endoscopic and histological findings in children aged 4-12, undergoing upper endoscopy for abdominal pain with dyspepsia in the teaching hospital Dr. Oscar Danilo Rosales Arguello, period 2007-2009". The main challenge in this activity was to correlate the thesis sections and article fields. It was necessary to choose the relevant data and to structure it according to the requirements of the article.

- **Creation of a Poster**

"A scientific poster is a communication tool which combines a verbal presentation with a visual aid" (55). The purpose of scientific posters is to present work to an audience who is walking through a hallway or exhibit (56). Posters should be considered a snapshot of your work intended to engage colleagues in a dialog about the work, or, if you are not present, to be a summary that will encourage the reader to want to learn more (57). These are the most common characteristics when people want to describe a scientific poster. When developing a poster, we have to take into account other skills that are not always present when writing a scientific article. It is very important to consider topics as (57):

    - **Title –** should be effective and quickly attract and orient the audience;
    - **Sections –** Their sequences should be well defined and easy to locate in the poster;
    - **Content –** Should be concise but the message must be clear;
    - **Time –** The poster should be short enough so it can be quickly read;

- **Visual aids –** Long sentences should be avoided and the use of images, graphs and drawings should be supported;

- **Others –** Several other points should be considered such as colours used, font type and size, background, spacing,

During my training period I had the opportunity to develop a poster, based on an article that assessed the indices of fat mass distribution when measured by dual energy x-ray absorptiometry in a Spanish healthy population. I had to read and extract the most important information of the article and transpose it into the format of a poster.
Thus, the development of a poster can be very challenging and exciting because it puts to a test a number of techniques and attributes that are often not needed in a more conventional writing, as is the case of a scientific article.

- **Development of content applied to Medical Marketing**

  Medical Marketing is the function that is responsible for developing and executing medical marketing strategies and tactics for a brand or therapeutic area. Medical Marketing connects the product's medical focus with its commercial aspects (58).
  This section intended to reflect the activities that gave support to commercial area, eg. for the development of proposals and planning activities. During the training period, the main task performed was data research, regarding specific topics, in order to find out what Novexem activity niche could be and the diversity of activities to propose.

  - **Atrial Fibrillation**

    It was a situation that required a simple research for the most updated information and guidelines regarding Auricular Fibrillation. This data was used to understand the current practices in this field and to establish Novexem *modus operandi* in relation to the presented proposals and activities.

  - ***Staphylococcus aureus* Infection and Surgery Wounds**

    In this case, it was requested to search for information regarding Portuguese statistics and guidelines about surgical site infections caused by *Staphylococcus aureus.* Information was varied, asking about infection rates, the existence or not of hospital infection committees and KOL, number of surgeries and ability of hospitals to perform *Staphylococcus aureus* cultures.
    This information had to answer to some pre-feasibility study questions in order to prove that Portugal would establish good centres with adequate recruitment

rates. The pre-feasibility questionnaire is a tool to help sponsors to decide where they should or not implement their studies.

- **Kras gene and Colorectal Cancer**

  This task required to search for the most updated information regarding the use of Kras mutation detection test. Recent data suggest an increasing use of this test for decision-making options regarding colorectal cancer treatment. In order to understand where Novexem could act, and what kind of proposals to develop, it is crucial to understand current practices and recommendations.

- **Ovarian and Pancreatic Cancer**

  This situation was very similar to the developed activity for *Staphylococcus aureus* infection and surgical wounds. It was necessary to answer some pre-feasibility questions regarding the healthcare centres for the treatment of ovarian and pancreatic cancer in Portugal.
  This information intended to demonstrate where care is provided for ovarian and pancreatic cancer and which type of oncologist and/or specialty cancer centres should be contacted by the sponsor in Portugal.

3. Discussion

Developing and presenting a training report can be very challenging, since it is unlikely to make justice to what really happened during this period. It is difficult to find the right words to describe all the knowledge, moments and lessons taken from this experience.

3.1. Tasks assigned

During my training period in Novexem Portugal, I was faced with the need to improve my time management skills and my ability in planning tasks.
Regarding the number of tasks, I believe I was given a big advantage over my colleagues as the tasks were being assigned to me, whenever possible, in a sequential way so I could focus on each one individually. However, this was not always possible. The basic principle of my training period was to try to perform different emerging tasks as I was training in different departments. This way, when there were new projects with important training tasks that I had never perform, I would accumulate these activities with those already in development.
Maybe the biggest challenge in developing the training tasks was the need to comply with deadlines. As a service provider, Novexem Portugal has the obligation to deliver the requested products on time, so I had to make an effort to adjust my working rhythm.
A very useful tool that helped me in this approach to time and task management was an electronic platform used in the company. In my profile it is basically a communication and task management tool where, among other things, I could track requirements and deadlines of different tasks and be aware of the developed and to be developed tasks.

Despite the rotating scheme planned between departments, the majority of tasks developed during the training period fell into two main departments:

- Medical Writing Department
- Clinical Operations

The predominance of these areas is related to my soft skills and because they are better suited to my academic background.

3.2. Learning Outcomes

Maybe more important than the developed activities, the ability to identify and achieve the learning outcomes were the main objectives in my training experience.
This training period allowed me to acquire and upgrade some of my hard and soft skills.

Hard skills

I was able to:

- Develop, review and criticize medical writing products as well as to get acquainted with tools, like programs for reference management, searching techniques in databases, among others;
- Prepare and conduct pre-study, initiation, monitoring and close-out visits;
- Understand and consult national and international regulations and guidelines;
- Develop and submit regulatory affairs' documentation;
- Understand and participate in Pharmacovigilance activities;

Soft skills

I was able to:

- Work as a team-member;
- Be independent and get autonomy;
- Develop critical thinking;
- Deal with great responsibilities;
- Be more organized;

All the presented outcomes were achieved or upgraded during my training period although the majority of them are still in development. This learning process, based on experience and close monitoring, is ongoing and will continue as I gain more experience. Several factors influenced this process and made it possible. My academic training was one of them. Both my graduation on Biomedical Sciences and now the Master's Degree in Pharmaceutical Biomedicine contributed to this process. A good example is the way tutorial sessions on my graduation influenced my ability to work as a team-member in Novexem. The brainstorming format of tutorial sessions helped me to adapt, since projects discussion meetings in Novexem follow the same pattern. The Masters course also had a pivotal role as it was very targeted and specific for pharmaceutical research and provided me with a very good background that I apply in different departments of Novexem Portugal, specially Medical Writing Department and Clinical Operations. Other fact that was essential for the acquisition of these skills/values was the continuous surveillance/guidance provided by workers from different departments in Novexem Portugal in every task. I was given autonomy for developing tasks but at the same time I was guided and taught, allowing me to fill my knowledge gaps.

3.3. Difficulties

I wouldn't call it difficulties but obviously there were some hurdles that I needed to overcome during this period. Although I consider my academic training very solid and specific for the activities to develop in Novexem, the first contact with a different reality is very intimidating and possibly makes you have second-thoughts about if you really are prepared and able to continue.

Communication and soft skills

My biggest challenges were my communication and soft skills. Being a shy and quiet person, sometimes, activities going beyond my comfort zone can be very challenging. Situations during my training period like the patients' Hotline Program and the clinical practitioner phone contact to perform opinion questionnaires, where communication is a crucial step, revealed themselves uncomfortable for me at the beginning. However, this was an excellent exercise to develop an area where I am not very strong at.

Time Management

As reported before, another challenge during these eleven months was the need to develop an activity within the agreed timeframes. This was especially true in medium-long term projects in medical-writing, because it was necessary to define mental steps alongside the available time in order to have the document/product ready for review/submission. If this does not happen, there is a risk of being devoting too much time to a certain section/step forgetting what also has to be performed, accumulating work and ultimately not being able to deliver it on time. For a few times I realized my tasks were accumulating. In order to solve this situation, I started to outline the necessary steps in each task I was assigned and estimate the time allocated to each one. This allowed me to have an overview of every task and to manage my time wisely.

Specific tasks issues

Not all the difficulties were related to me. Sometimes they just occur and there is nothing you can do but try to move forward. It was the case of some projects that presented some issues, namely:

- The difficulty to meet clinical practitioners in order to explain the project and convince them to participate;
- The lack of requirements from the sponsor when asking for project proposals;
- The lack of feedback from sponsors when needed to develop the project;

4. Conclusions

This document intended to present the activities developed during my training period in Novexem Portugal, as well as all the learning outcomes and skills acquired during this journey.
This experience was very useful as it allowed me to apply the knowledge acquired in the Master's Degree in Pharmaceutical Biomedicine in real situations of the working life and also to absorb the whole experience, its gains and lessons.
The Master's Degree in Pharmaceutical Biomedicine in collaboration with different companies in pharmaceutical research area contributed to the academic education of students, combining theoretical training with human and attitudinal skills and giving us the ability to solve very specific professional problems in working teams.
Novexem Portugal continued the teaching process and companies like Novexem are ideal partners of the Masters course as they help to fill the gaps of students in a personalized and efficient way.

I did not have the opportunity to develop activities in all departments, but in those where I went to I have a solid training. I learned how to produce/review/submit medical writing products, how to prepare/conduct pre-study/initiation/monitoring/close-out visits, to understand and consult national and international guidelines and regulation, how to develop and submitting RA' documentation and to understand and participate in Pharmacovigilance activities.

Thus, I believe all the training period objectives initially proposed were fully achieved. I was able to start a network of contacts that are influent in clinical research area and the mentioned difficulties were overcome.

Looking back, I can conclude that the Master's Degree in Pharmaceutical Biomedicine provided me a very good background with wide applicability in the real world of scientific research, especially in the field of clinical monitoring, clinical studies and related guidelines and regulations. This academic background allowed me to integrate more quickly and to understand the processes underlying each task.

This experience also allowed me to have a different opinion regarding pharmaceutical industry and clinical research and to clarify punctual misinterpretations from master course classes.

Currently I'm exerting functions at the Medical Writing Department and also as a CRA. I've been offered a position in the company for one additional year, starting in September, performing the abovementioned functions and I'm really looking forward to it.

The opportunity that was given to me, to do my training period in Novexem Portugal, proved to be very fruitful and gratifying.

5. References

1. Faber A, editor. The market of medicines and biological products. Training Programme in Pharmaceutical Medicine - The Healthcare Marketplace; 16 December 2011; INFARMED, Lisbon.

2. Outsource2India. A Global Pharmaceutical Industry Report. 2011 [cited 2011 May 23]; Available from: http://www.outsource2india.com/kpo/samples/pharmaceutical-industry-report.asp.

3. Health I. IMS Market Prognosis 2010.

4. Office CB. Research and Development in the Pharmaceutical Industry 2006.

5. FitzGerald G. Perestroika in Pharma: Evolution or Revolution in Drug Development. Mount Sinai Journal of Medicine. 2010;77:327-32.

6. Checkonomics. Pharmaceuticals. 2010 [cited 2011 July 8]; Available from: http://www.checkonomics.com/IndustryOverview.aspx?IID=51&CAT=106CC612&IName=Pharmaceuticals&CatName=Trends.

7. EvaluatePharma. World Preview 2016 2010.

8. Bennani Y. Drug discovery in the next decade: innovation needed ASAP. Drug Discovery Today. 2011.

9. Wilsdon T, Atridge J, Chambers G. Current state of innovation in the pharmaceutical industry. CRA International; 2008.

10. PWC. 2011 [cited 2011 July 10]; Available from: http://www.pwc.com/gx/en/annual-review.

11. NGP. Evaluating Challenges to Clinical Trial Execution. NGP - Next Generation Pharmaceutical. 2006.

12. Carlson PE. Clinical Research Industry Trends2007.

13. Markets Ra. The CRO Market Outlook: Emerging Markets, Leading Players and Future Trends. 2009 [cited 2011 May 23]; Available from: http://www.researchandmarkets.com/reports/541346/the_cro_market_outlook_emerging_markets_leading.

14. Zhang J. The Future of the Pharma Outsourcing Industry After the Financial Crisis. Life Science Leader. 2010.

15. ISO. ISO 9000 essentials. 2011; Available from: http://www.iso.org/iso/iso_9000_essentials.

16. WHO. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool 2006.

17. Decreto Lei nº 176/2006 de 30 de Agosto - Estatuto do Medicamento, (2006).

18. Lei nº 46/2004, de 19 de Agosto, (2004).

19. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, (2001).

20. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, (2001).

21. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 21 March laying down community procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, (2004).

22. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, (2010).

23. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, (2010).

24. EMA. New 2010 pharmacovigilance legislation. 2011 [cited 2011 June 10]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058033e8ad.

25. EMA. European Medicines Agency - Science Medicines Health. 2011 [cited 2011 May 16]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp.

26. EMA. CHMP: Overview. 2011 [cited 2011 June 10]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7a&jsenabled=true.

27. International Conference on Harmonisation (ICH). Vision about ICH. 2011 [cited 2011 June 10]; Available from: http://www.ich.org/about/vision.html.

28. CIOMS. Council for International Organizations of Medical Sciences. 2011 [cited 2011 June 10]; Available from: http://www.cioms.ch/.

29. Robson AS, Bawden D, Judd A. Pharmaceutical and Medicines Information Management - Principles and Practice. Livingstone C, editor: Harcourt Publishers Limited; 2001.

30. Jacobsen TM, Wertheimer AI. Modern Pharmaceutical Industry: A Primer: Jones and Bartlett Publishers; 2010.

31. do Vale MCJP. Estudos Observacionais: CEIC - Comissão de Ética para a Investigação Clínica, [cited 2011 June 10].

32. EMA. Telematics Programme. 2011 [cited 2011 June 10]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000116.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c2b.

33. CEIC. CEIC - Missão. 2011 [cited 2011 May 24]; Available from: http://www.ceic.pt/portal/page/portal/CEIC/QUEM_SOMOS/MISSAO.

34. CNPD. O que é a CNPD. 2011 [cited 2011 May 24]; Available from: http://www.cnpd.pt/bin/cnpd/acnpd.htm.

35. ISPE. International Society for Pharmacoepidemiology. 2011 [cited 2011 July 10]; Available from: http://www.pharmacoepi.org/.

36. International Conference on Harmonisation (ICH). Topic E2E on Guidance for Industry - Pharmacovigilance Planning. London: European Medicines Agency, 2004.

37. Liu MB, Davis K. A Clinical Trials Manual from the Duke Clinical Research Institute: Wiley-Blackwell; 2010.

38. International Conference on Harmonisation (ICH). Topic E 6 (R1) for guidance on Good Clinical Practice. London: European Medicines Agency, 2002.

39. Associates DSE. Queries in Clinical Trials. 2011 [cited 2011 July 11]; Available from: http://drugsafetyexpert.com/queries-in-clinical-trials/.

40. Abdel-Aleem SM. Design, Execution, and Management of Medical Device Clinical Trials. Wiley, editor 2009.

41. European Medical Writers Association E. Medical Writing 2009.

42. AMWA. American Medical Writers Association. 2011 [cited 2011 July 11]; Available from: http://www.amwa.org/default.asp?id=1.

43. Association AMW. Australasian Medical Writers Association. 2011 [cited 2011 July 11]; Available from: http://www.medicalwriters.org/.

44. EMWA. European Medical Writers Association. 2011 [cited 2011 July 11]; Available from: http://www.emwa.org.

45. IMWA. Indian Medical Writers Association. 2011 [cited 2011 July 11]; Available from: http://www.freewebs.com/imwa/.

46. Gad SC. Clinical Trials Handbook: John Wiley & Sons, Inc.; 2009.

47. NCBI. PubMed Help. 2011 [cited 2011 May 12]; Available from: http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Quick_Start.

48. Batovski DA. How to write a review article. Assumption University Journal of Technology. 2008;11(4).

49. Hmelo CE, Ramakrishnan S, Day RS, Shirey WE, Brufsky A *et al*. Oncology Thinking Cap: Scaffolded Use of a Simulation to Learn Clinical Trial Design. Teach Learn Med. 2001;13(3):183-91.

50. Piantadosi S. Clinical Trials - A Methodologic Perspective. 2nd ed: John Wiley & Sons, Inc.; 2005.

51. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials: Springer; 2010;1:9.

52. Lo B. Ethical Issues in Clinical Research: A Practical Guide: Lippincott Williams & Williams; 2010;6:46.

53. Derenzo E, Moss J. Writing Clinical Protocols - Ethical Considerations: Elsevier Ltd.; 2006; 8:133.

54. Kerr DJ, Knox K, Robertson DC, Stewart D, Watson R. Clinical Trials Explained - A Guide to Clinical Trials in the NHS for Healthcare Professionals. Blackwell Publishing Ltd.; 2006.

55. Kirkeby KA. Preparing Professional Scientific Posters. Available from: http://www.ce.umn.edu/~smith/supplements/poster/guide.htm.

56. Design pf Scientific Posters. 2008 [cited 2011 14 May]; Available from: http://www.writing.engr.psu.edu/posters.html.

57. Erren TC, Bourne PE. Ten Simple Rules for a Good Poster Presentation. PLoS Comput Biol. 2007;3(5):e102.

58. Freedman T. Career Opportunities in Biotechnology and Drug Development. Press CSHL, editor 2008.