Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2011

Joana Caria Caetano da Silva

Relatório de estágio curricular na Bayer Portugal.

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da professora Doutora Alexandra Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro.

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Vogal	Dr.ª Isabel Fonseca Santos Bayer

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palavras-chave

Ciências Biomédicas, Biomedicina Farmacêutica, Ensaios Clínicos, Estudos Observacionais, Indústria Farmacêutica, Farmacovigilância, Assuntos Regulamentares, Market Access.

Resumo

Os profissionais de biomedicina farmacêutica estão aptos a seguirem o processo de desenvolvimento de um medicamento em todas as suas fases. A formação académica nesta área, proporciona também ao estudante, o conhecimento para monitorizar a segurança do medicamento, preparar o dossier regulamentar necessário para o pedido de autorização de introdução no mercado e para avaliar se, durante a comercialização, todos os aspectos éticos e legais estão a ser cumpridos.

O objectivo deste estágio no departamento médico da Bayer Portugal foi colocar em prática os conhecimentos e competências adquiridas durante o primeiro ano do mestrado. A monitorização de estudos observacionais foi a principal actividade desenvolvida neste departamento. Contudo, a oportunidade de experimentar outras áreas foi igualmente possível graças a uma curta rotação por outros departamentos onde eram desempenhadas outras funções e nos quais foi ministrada alguma formação. Este estágio proporcionou uma visão clara e abrangente de como funciona uma empresa farmacêutica e de quais os papéis que o profissional em biomedicina farmacêutica aí pode desempenhar.

keywords

Biomedical Sciences, Pharmaceutical Medicine, Clinical Trials, Non-Interventional Studies, Pharmaceutical Industry, Pharmacovigilance, Regulatory Affairs, Regulatory Affairs, Market Access.

abstract

Pharmaceutical Medicine professionals are capable of following the drug development process through all its phases. Academic training on this are also provides the student with the knowledge to monitor the medicines safety, to prepare the regulatory package needed to request marketing authorization and to evaluate compliance with legal and ethical aspects during marketing of the product. The objective of the on job training at the Medical Department of Bayer Portugal was to put into practice the concepts and competences gained during the first school year of the masters' degree. Monitoring non-interventional studies was the main activity developed in the department. The opportunity to experience other areas was also possible due to a short job rotation on several other departments where a small training was also given. This internship provided a clear and comprehensive vision of how a pharmaceutical company works and of the several roles a pharmaceutical medicine professional may play on it

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Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
APIFARMA	Associação Portuguesa da Indústria Farmacêutica *(Portuguese Association of the Pharmaceutical Industry)*
ASR	Annual Safety Report
BHC	Bayer Healthcare
CA	Competent Authority
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CEIC	Comissão de Ética para a Investigação Clínica (*National Ethics Committee for Clinical Research*)
CF	County File
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CLM	Country Lead Monitor
CNPD	Comissão Nacional para a Protecção de Dados (*National Committee for Data Protection*)
COX-2	Cyclooxygenase-2
COV	Close Out Visit
CRA	Clinical Research Associate (also know as monitor)
CRF	Case Report Form
CTA	Clinical Trials Assistant
CV	Curriculum Vitae
DGAE	Direcção – Geral das Actividades Económicas (*Directorate-General for Economic Activities*)
EC	European Commission
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
e.g.	exempli gratia
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practices
GDP	Gross Domestic Product
GIDEON	Global Investigation of therapeutic DEcision in hepatocellular carcinoma and Of its treatmeNt
GPV	Global Pharmacovigilance
HCC	HepatoCelular Carcinoma
HCP	Healthcare Professional
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Reports
ID	Identification
i.e.	id est
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INFARMED	National Authority for Medicines and Health Products
INN	International Non-proprietary Name
IRB	Institutional Review Board
ISF	Investigator Site File
KOL	Key Opinion Leader
LDSMD	Local Drug Safety Manager Deputy
LHMStm	Local Head of Monitoring and Study management

LODE	Lack Of Drug Effect
LQR	Local Quality Representative
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MD	Medical Department
MP	Monitoring Plan
NHS	National Health Service
NIS	Non-Interventional Studies
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OECD	Organization for Economic Co-operation and Development
OS	Overall Survival
OTC	Over-The-Counter
PASS	Post-Authorization Safety Studies
PFS	Progression Free Survival
PhRMA	Pharmaceutical Research and Manufacturers of America
PMV	Periodic Monitoring Visit
PMVR	Periodic Monitoring Visit Report
PSUR	Periodic Safety Update Report
PTC	Product Technical Complaint
PV	Pharmacovigilance
PVCH	Pharmacovigilance Country Head
RA	Regulatory affairs
RAM	Regulatory Affairs Manager
R&D	Research & Development
SA	Scientific Adviser
SAE	Serious Adverse Event
SDV	Source document verification
SIF	Site Information Form
SIV	Site Initiation Visit
SOP	Standard Operating Procedures
SPC	Summary of product characteristics
SSV	Site Selection Visit
SSVR	Site Selection Visit Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Therapeutic Area
TMF	Trial Master File
TTP	Time To Progression
USA	United States of America
VTE	Venous Thromboembolism
XAMOS	Xarelto® in the prophylaxis of post surgical venous thromboembolism after elective major orthopedic surgery of hip or knee
WHO	World Health Organization

1. Introduction

1.1. Executive Summary

Integrant part of the masters in pharmaceutical biomedicine the purpose of this internship was to provide on the job training that would allow contact with the pharmaceutical industry setting and to put into practice the concepts and competences gained in this scientific area during the masters. This internship was held in the Medical Department (MD) of Bayer Portugal, SA on its facilities in Carnaxide, in the outskirts of Lisbon during the second year of the master's degree. It started in September 1st 2011 and lasted for ten months.

1.2. Objectives

In the internship first weeks there was a welcome program comprising a basic introduction to Bayer HealthCare (BHC) Portugal, where it was possible to get to understand how the company was organized and the people who worked there.

During this initial period there was also a training stage on the applicable Standard Operating Procedures (SOPs); study protocols; study case report forms; pathologies and medicines which were being investigated in the Non-Interventional Studies (NIS).

The on the job training was then divided in to two main components:

- Permanent monitoring activities of NIS;
- Observation, training and experimentation of other areas of the company.

Once a month for a period of one week, the rotation in the other departments was held for about four hours, which let time for carry out the necessary monitoring activities for part of the day. This hands on training understood the scientific advisory, pharmacovigilance, clinical operations, regulatory affairs, market access and medical marketing fields.

1.3. Report Structure

This internship report is comprised by 5 chapters, including this introduction were an executive summary together with the objectives of the internship are provided.

The second chapter starts by providing the state of the art and a brief overview of the Portuguese healthcare market, followed by a portrayal of the host organization, particularly of the medical department. It also entails a section on the Scientific Adviser, Medical Information and Medical Marketing roles.

A description of the main activity performed monitoring of Non-interventional studies is given in the third chapter. In this section there is a definition of this type of studies, their role in the development

process of a medicinal product, procedures and quality review activities. The process of medical writing and development activities of a NIS protocol is also provided in this chapter.

From the fourth chapter on there is a characterization not only of the area of the departments where I was able to perform a job rotation but also of the activities I perform during that time.

Chapter 4 includes a discussion of the main gains and difficulties from the activities I performed during this internship.

Finally a conclusion is provided where the value of the Medical Department is once more stated as well as the importance of the pharmaceutical biomedicine professional.

2. Host Organization Characterization

2.1. State of the art

Over the last few years, European countries have achieved major improvements in their health statuses. In Portugal's case, heath indicators such as average life expectancy at birth increased since 1980's and in 2006 reached 79.0 years, whereas that for the EU15 group was 80.31 years (1, 2).

Improvements seem associated with numerous factors:

- Better living and working conditions;
- Increases in human and material resources devoted to healthcare;
- Higher budgets and spending allocated for healthcare systems;
- Better socioeconomic conditions;
- Reducing risk factors as tobacco and alcohol consumption (1, 2).

But one must not forget the impact of the recent progresses in medical care and therapeutics, for which the pharmaceutical industry is a major contributor. Prescription medicines have enhanced quality of life for many people by preventing diseases, reducing disability, slowing disease progression and extending life (3). High blood pressure can be controlled with antihypertensive medicines and some cancers can be controlled or even cured thanks to new targeted therapies.

The pharmaceutical industry is responsible for turning fundamental research into innovative treatments that will be available and accessible to patients. But some disease areas such as Alzheimer, many cancers or orphan diseases, still remain a challenge (3).

However there is also the need to find out if the gains in life expectancy actually involve additional years of life lived with good health and the implication to health systems of this augment. As a result of better living conditions and changes in lifestyle like a more sedentary regimen, conditions such as obesity now affect more than half of the European population and are associated with a broad series of health issues varying from diseases such as type-2 diabetes, dyslipidemia, and hypertension to impaired quality of life that are considered chronic illnesses and increase direct costs and expenditure to the countries health systems (1, 4).

Another consequence of the increase in the life expectancy in Portugal together with a drop in the fecundity rate is the fact that the population is aging. The percentage of older people has raised to 17.3%, while the fecundity rate is now below the Organization for Economic Co-operation and Development (OECD) average of 1.65 (1).

Ageing populations have shown an increase in the prevalence of chronic diseases as asthma, chronic bronchitis, diabetes, congestive heart failure, arthritis, cardiovascular disease, lung problems and diabetes (5).

Thanks to the IT advent and the easy access to new sources of information, patients are now demanding more and better medicines and taking a more active part in their health decisions, which results in the use of even more health services.

Health systems are now spending more on health than never thanks to all these factors and Portugal is no exception to this.

The Portuguese Healthcare System is constituted by the National Health Service (NHS), a conjunct of public insurance schemes for certain professions, also known as health subsystems and by voluntary health insurance.

Portugal's system is funded mostly by public capital, through taxes, but there is also private financing, mainly in the shape of out-of-pocket payments by patients and private health insurance. Health Care can be provided either by public or private institutions.

The NHS is divided into primary care, hospital care, continued care and agreements in fields such as haemodialysis with private providers.

Health expenditure in Portugal is about 10% of the gross domestic product, in which 21% is estimated to be costs with pharmaceutical spending, so in the last few years there have been several pharmacopolitical measures implemented by the governments that aimed at containing those expenses (1, 6, 7).

These measures included among others, free availability of generics to low-income pensioners, changes in the reimbursement system, promotion of generic use, adjustments in the distribution margins and electronic prescribing system of medicines (8).

The Portuguese NHS has also been suffering a restructuration in order to achieve cost efficiency that included the creation of family health units, the administrative junction of several hospitals and conception of public health units with financial autonomy.

Hospital administrations are now creating treatment protocols and demanding a more rational prescription of medicines and complementary diagnostic media from their physicians.

When deciding with the hospital pharmacy if they are going to purchase a new medicine, they are now asking for health economic studies and for price-volume agreements.

Marketing authorization applications are now taking less time in Portugal (about 166 days for the national MA on the first semester of 2011), contrasting with the process for access to reimbursement, which is becoming tougher, and lengthier (in average 437 days), delaying market entry and wasting precious patent protection period (9, 10). The government has revised the reference price system whilst making comparisons with international medicines prices and demanding more pharmacoeconomic studies that many times are difficult to compose because of the lack of data published in and about Portugal (9).

The Portuguese pharmaceutical market is mainly dominated by multinational companies such as Bayer. In 2008 there were 138 pharmaceutical companies acting in Portugal employing 10.244 persons (6).

The human pharmaceutical market is divided into prescription-only and over-the-counter (OTCs) medicines both generic and from innovation companies, which can be found in both the ambulatory and hospital market.

In 2009 the medicines total market value (ambulatory market + hospital market) was 4.727.901€ and the NHS spent 1.565.468€ with medicinal products (6).

Nowadays there are several challenges for innovation pharmaceutical companies such as Bayer. Research & Development (R&D) costs of a new medicine are very high and at least 50% of experimental medicines fail in phase III studies (11). In the USA only about one in six drug candidates are ultimately submitted and approved by the FDA and in Europe on 2009 only 29 new active substances were recommended by CHMP for marketing authorization through the centralised procedure (3, 12).

The development phase of new medicines also lasts for 10 to 15 years time (Figure 1). During this period researchers work to:

- validate targets by studying for example, causes of disease at the level of genes, proteins and cells;
- discover the right molecule (potential drug) to interact with the target chosen;
- test the new compound in the laboratory and clinic for safety and efficacy; and
- gain approval and get the new drug into the hands of doctors and patients (13).

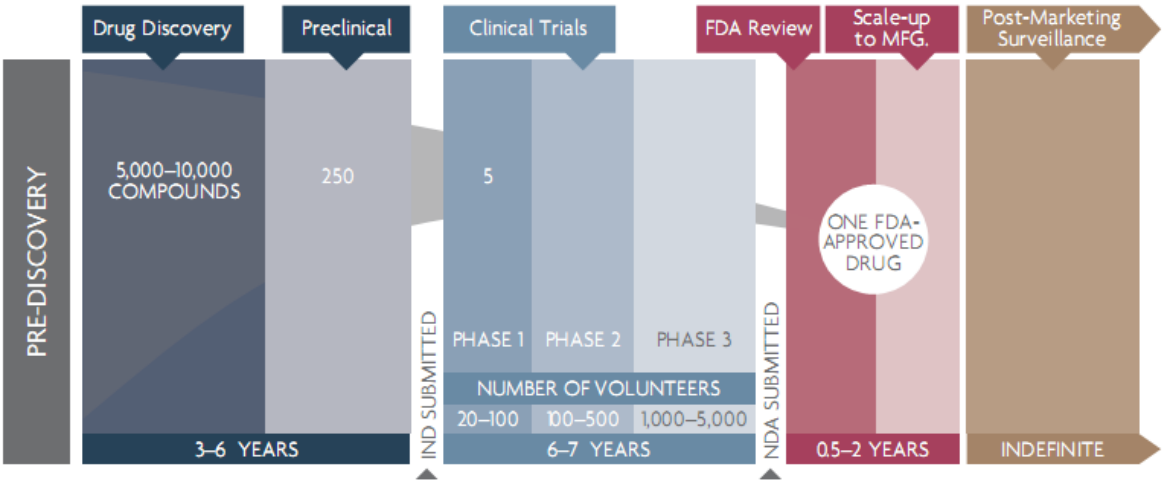


Figure 1. Example of a medicinal product research and development process (14)

Merges and other business strategies also reduce the number of potential successful candidates (15).

There is still a trend to research easy targets focusing in chronic diseases with large potential markets, such as hypertension or depression that would become sales blockbusters.

The complexity of development and its associated costs have risen exponentially and they are waning investor confidence. Clinical Trials are increasingly bigger, more complex and time consuming, as Table 1 shows, Eligibility criteria for volunteers are even narrower which has been leading to a lower recruitment and retention rates (3).

Several pharmaceutical companies have also been abandoning starting clinical trials in Portugal, because of the low recruitment rates and of the time hospital administrations and competent authorities take to approve said trials.

Table 1. Changes in Clinical trials: resources, length and participation (14)

	1999	2005	Percentage Change
Procedures per trial protocol (median) (e.g bloodwork, routine exams, x-rays...)	96	158	65%
Clinical trial staff work burden(measured in work-effort units)	21	35	67%
Length of Clinical Trial (days)	460	780	70%
Clinical trial-participant enrolment rate (%of volunteers meeting trial criteria)	75%	59%	-21%
Clinical trial-participant retention rate (%of participants completing trial)	69%	48%	-30%

Nevertheless there still are reasons to be optimistic and measures have been put into practice to solve some of these problems. One of the strategies implemented have been the creation of public-private partnerships, the Critical Path Initiative by the FDA and the Innovative Medicines Initiative by EMA (16). These two programs were intended to:

- improve the likelihood of success of new drugs being developed;
- identify new and more efficient research methods;
- encourage development of medicinal products that respond to unmet health needs, as the example of many orphan disease that only affect a small patient population;
- support the use of better evaluation tools such as biomarkers and disease models;
- simplify clinical trials, using for example adaptive study designs;
- study special populations as the paediatric (16).

Nowadays there is also a growing concern with the safety of medicines. In Europe, for example, a new pharmacovigilance directive has been approved and risk minimization plans are becoming obligatory for most medicines (17). This new directive is supposed to be implemented until 2012.

2.2. Host organization characterization

Bayer Healthcare (BHC) is one of the business subgroups of Bayer A.G., which operates and has sites in all five continents.

In Portugal it is managed by Bayer Portugal, SA together with the other company's subgroups- Bayer Cropscience and Bayer Material Science.

The Portuguese headquarter is situated in Carnaxide near the country's capital Lisbon. BHC objective is to research, develop, manufacture and market innovative products which will improve

the health and quality of life of people and animals worldwide through the prevention, diagnosis and treatment of diseases putting into action its mission of science for a better life.

This business subgroup is divided into four divisions:

- Pharmaceuticals – responsible for researching and developing new therapies;
- Consumer Care – in charge of over-the-counter(OTC) or non-prescriptions drug market;
- Medical Care – with a portfolio among other things of blood glucose meters;
- Animal Health – specialized in veterinary medicines for companion animals and live-stock (18).

The Portuguese Pharmaceuticals division is constituted by two business units – General Medicine and Specialty Medicine.

These units are focused mainly in therapeutic areas (TA) where there still is medical need such as oncology, diagnostic imaging, cardiovascular and haematological disorders, neurology, women's health (gynaecology and contraception) and men's health (e.g. erectile dysfunction).

Also part of the Pharmaceuticals division is the Market Access department which interact closely with the business units.

Regulatory Affairs department as the Medical department offer support to all business units. Regulatory Affairs also has the peculiarity of offering technical and regulatory support to the Animal Health division.

Bayer Portugal is also composed by supporting departments such as Controlling and Administration Office, Human Resources, Information Technology Support and Legal.

Bayer has been established in Portugal for more than 100 years and according to a Brand Reputation Index from Marktest, among the Portuguese Pharmaceutical Sector it is the most recognized brand and it is on the twenty seventh place overall (19).

The company is also in the top ten of the leading pharmaceutical corporations in Portugal, occupying the seventh place in terms of sales (20).

2.2.1. The Medical Department

Portugal's Medical Department (MD) mission is "putting patients first" while also providing a strong scientific backbone to the company. This department acts as BHC's medical conscience, thus one of its major roles is to keep the company aware of the needs of the patients and of the healthcare professionals (HCP).

The MD main areas of responsibility are to:

- Ensure compliance to legal requirements and guidelines;
- Provide a medical perspective to product development;
- Provide the medical input to the support of marketed products throughout their life cycle;
- Provide specialised medical and scientific expertise;
- Act as the company expert interface with HCPs.

The Portuguese MD is headed by the medical director, Dr. Isabel Fonseca Santos, a pulmonologist and pharmaceutical physician, who is supported by a group consisting of other physicians, pharmacists, life scientists (biology and biotechnology graduates) and administrative staff.
Within the MD, these professionals take the roles of:

- Scientific Advisers (SA);
- Drug Safety specialists;
- Scientific information Manager;
- Clinical Trials Manager;
- Clinical Research Associates (CRA also known as monitors);
- Clinical Trials Assistants (CTA);
- Medical Consultants.

MD is organized according to the Figure 2 into Medical Affairs and Clinical Operations.
The medical director is responsible for and administrative management of Clinical Operations (Clin Ops),which is managed by a Local Head of Monitoring and Study management for Portugal and Spain, from this last country. This unit is in charge of the initiation and monitoring of clinical trials sponsored by BHC in Portugal.
Scientific Advisers are another of the functions under the direct management of the medical director. These professionals provide specialized information and support to one or more therapeutic areas for external and internal stakeholders (HCPs and marketing and sales colleagues respectively). The scientific information specialist is responsible for answers to all other scientific or medical inquiries that are not designated to any SA.
Dr. Isabel also acts as the nominated qualified person responsible for pharmacovigilance (PV) for Bayer Portugal products in Portugal. To help her with drug safety activities she has the aid of a deputy and together they handle all the safety information coming from clinical trials and medical information.
MD is also responsible for the management and coordination of non-interventional studies (NIS).
As the medical affairs department trainee I was under the management of the medical director and the supervision of the SA responsible for the NIS I was working with.

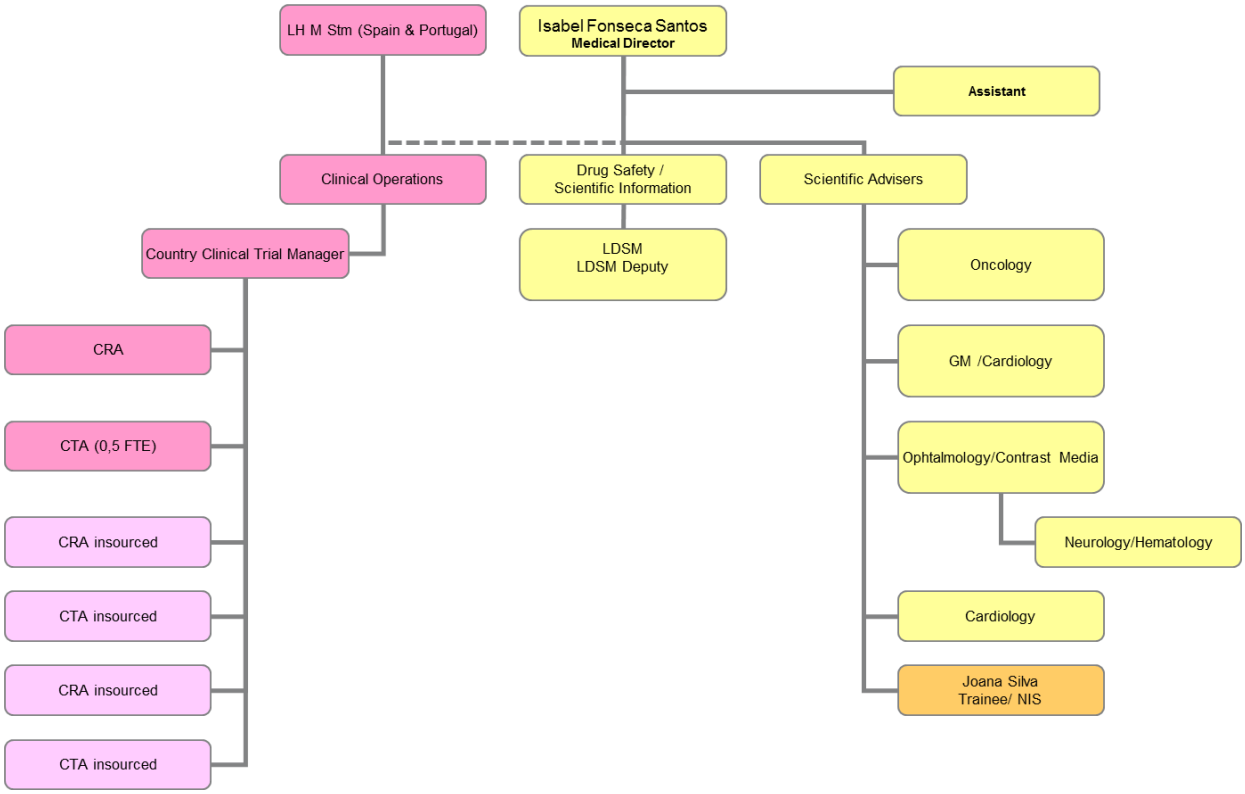


Figure 2. Bayer Healthcare Portugal Medical Department Organigram

Although the medical department is a team on itself, its members are part of other cross-functional groups where they interact with colleagues from other departments such as marketing & sales and regulatory affairs.

It is important that all departments' members effectively communicate with each other and work together to maintain the company scientific and ethical standards. To facilitate this, all members of the MD meet on a monthly basis to keep one another's updated on their main activities, recent scientific advances for their TA and to inform on important medical and scientific scheduled events. This meeting also serves as an important liaison between the SAs and the clinical operations unit enabling them to exchange information on status of recruitment; participating centres and investigators; and to swap opinions on new studies.

During these meetings there is also a journal club, where one of the department members chooses one theme that he/she thinks may be interesting to share with the others, and does a presentation on it. This allows for a scientific enrichment of the team. In one of these meetings I was responsible for preparing one of the medical department journal club presentations (Appendix I - Adaptive Study Designs Presentation). The topic I chose was adaptive trial designs and the following topics were addressed:

- Current R&D paradigm
- Critical Path and Innovative Medicines Initiatives
- Adaptive Design
- Types of adaptation

- Types of designs
- Ethical and regulatory considerations.

Since MD is responsible for ensuring the scientific expertise of the company, it was considered important to provide a continuous training on the several TA to the members of the management team. In order to accomplish so MD, organizes the “early bird training sessions”. Each session is about two hours long and comprehends not only a presentation by one of the MD team members but also one from a colleague from one of the other departments (usually marketing). I was able to attend sessions on:

- Oncology – Nexavar;
- Rivaroxaban – Rocket – AF study;
- Rivaroxaban - Einstein DVT and Extension;
- Levitra ODT;
- Kogenate;
- Pulmonary Hipertension – Riociguat.

2.2.1.1. Scientific Adviser, Medical Information and Medical Marketing

Since the publication of the first ethical code on interactions with healthcare professionals, the relationship between drug companies and prescribing health professionals changed and rules were written about the use of informational presentations, educational meetings, employing physicians as consultants, speaker training meetings, and promotional give-away items.

Medical Affairs departments were first established to facilitate peer-to-peer interactions between prescribing physicians and company representatives who were doctorate-level scientists, pharmacists, and physicians. Medical Affairs employees were tasked with discussing the science behind the products and were trained to deal with highly technical information (21).

Nowadays Medical Affairs role is evolving and gaining more responsibilities.

One of the key players in this setting is the scientific adviser (SA). This professional is a resource of education and scientific knowledge with high expertise, who interacts not only with other departments of the company, such as regulatory affairs or marketing, but also with external stakeholders, for example, healthcare professionals , patients associations, media, regulatory authorities.

In BHC, SA main responsibilities are

- interaction with Key Opinion Leaders (KOL);
- coordination of non-international studies (NIS);
- support to investigator sponsored studies (ISS);
- scientific exchange activities such as clinical sessions, participation in congresses and scientific meeting, and organization of symposia.

SAs at BHC at this company are structured according to TA, specifically in oncology, neurology, contrast media, haematology, cardiovascular area and women’s’ healthcare (Figure 2).

A SA is also responsible for sales team scientific training, product launch support and preparation and review of promotional materials.

While reviewing promotional materials, SAs must ensure that these are corroborated with the most actual and accurate scientific information available and are in compliance with the EFPIA code (22).

Analysis of the market and anticipation of trends and difficulties is also one of its duties. This analysis is usually part of the annual Medical Affairs Plan that each SA has to organize for each of its TA. I participated in the preparation of the 2011 and 2012 Ophthalmology Medical affairs Plan. This plan states:

- Key timelines;
- Objectives for this TA;
- Performance and KPI's;
- Global Clinical Development ongoing and planned clinical trials / studies;
- Ongoing and planned NIS/phase IV studies;
- ISS strategy;
- Ongoing and planned registers;
- Ongoing and planned projects;
- Advisory boards;
- Local publications/abstracts;
- Activities around national meetings, symposia and congresses;
- Activities around international meetings, symposia and congresses;
- Training Bayer employees (who and when);
- Training Professionals (who and when).

Through the Medical Information Service, SAs act as a source of expertise and accuracy when answering to queries of HCP and consumers on clinical and safety aspects of the product with specialized and customized information.

The first line of communication of R&D results is also made through the SA, mainly in the form of clinical sessions. These sessions are usually performed at hospital services and the target audience is made of specialists physicians of the therapeutic areas for which the medicinal product has been approved. I had the opportunity to attend clinical sessions on the orthopaedic area where the target audience was made of orthopaedists. In this clinical session the main R&D results were presented together with the pharmacokinetics, adverse events and mechanism of action of the medicinal product being presented. I also attended several contrast media clinical session with audiences that would include radiology students or radiologists and pharmacists.

Very often SAs participate in BHC international meetings and symposia, which are a great way to exchange practices and knowhow with colleagues from around the world and collaborate in the definition of investigation strategies.

At BHC Portugal, the SA works closely with the marketing colleagues of their therapeutic area, even sharing the same office when possible. This allows for an enhanced collaboration with the marketing team, a better development of brand messaging strategies, an alignment of activities and a better understanding of the scientific needs. SA also participates in the marketing cycle meetings where they often take the opportunity to give training to the sales team on the latest scientific articles and information available. I was able to participate in three specialty medicine business unit cycle meetings and in one meeting for general medicine. For the specialty medicine meeting I would usually prepare a power point presentation that would be presented by the SA responsible for that area on the NIS recruitment and patient status. In these meetings I also had the chance to learn more about the business aspect of each TA and how the marketing plans and communication strategies are step up.

SAs also provide product launch support by participating in international and local meeting about the launch of the product. In BHC Portugal for a new ophthalmology product that will be launched, a launch team was created that meets in a monthly basis. I was able to participate in these meetings that have the purpose of preparing a successful entry of this new product on the market. The medical affairs members of these meetings are responsible among other things for:

- profiling KOL and set-up individualized communication programs for them;
- defining scope and timing of medical information materials such as scientific slide sets, standard response or medical scientific Q&As;
- communicating R&D results to KOL;
- preparing Advisory Boards.

Advisory Boards are often organized by the SA of the respective TA. These meetings serve to assemble a panel of experts/KOL to gather their opinions on specific medical/scientific questions of a certain product. For example, an advisory board may be held to discuss recently published R&D results of a new product or to collect information on the usual practices of a specific medical field.

While preparing an Advisory Board, one must first define which persons will be invited to join it and who will be the chairperson of the meetings. The main KOLs should be part of the group of invitees, since their involvement enhances the scientific relevance of the meeting..

During this internship I had the opportunity to participate on the preparation of one advisory board and to attend it. I was also able to accompany SA on some of their visits to KOL.

At some points during my job rotation I was also able to perform the bibliographic research needed to answer medical queries, on themes such as the following:

- Chemoembolization and HCC publications from Portuguese experts;
- Cardiac perfusion and Gadovist;
- Compassionate use (Appendix II - Compassionate Use Presentation);
- Gadovist, paediatric use and hemodiafiltration.

3. Activities description

3.1. Main activity - Non-Interventional studies management

A Non-Interventional study (NIS) according to Directive 2001/20/EC is defined as: 'a study where the medical product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (23). These studies may also be referred as phase IV studies, since they are conducted when the drug is already in the market.

The aim of this type of study is to provide an exclusive perspective of the medicine's actual usage compared with the recommended one that resulted from clinical trials.

NIS also allow a real world practice and outcomes perspective, that cannot be gathered from clinical trials where a treatment allocation and an well-defined patient population that excludes patients in virtue of some characteristics distorts routine clinical practice and lacks generalizability, since it cannot be applied to other subpopulations.

From a drug safety and pharmacovigilance point of view these studies are also very important, and are becoming part of risk minimization plans and one of their subtypes, PASS (Post Authorization Safety Study), is nowadays often required on the initial approval of the drug by the regulatory authorities (24).

NIS allow to identify and evaluate uncommon or delayed adverse events, with event rates of concern less common than 1:2000-3000 that otherwise would be difficult to recognize in clinical trials. Clinical trials also have limitations when trying to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or to identify certain risk factors for a particular adverse event. In these cases NIS may be the only practical choice, because normally they follow-up patients for a more extended duration than clinical trials, in a real world setting. NIS also allow to separate more properly the side effects caused by the disease being treated from those of the concomitant medication and disorders or from those of the medicinal product being studied.

NIS are a valuable instrument to gather more reliable data about the effectiveness and safety of medicinal products in real life in order to not only improve treatments but also patient care.

There are three types of non-randomized non-interventional studies: pharmacoepidemiologic studies, registries, and surveys (25).

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.

The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. This type of

studies is designed to assess the risk attributed to drug exposure, so they have a protocol and test a prespecified hypothesis. They also allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse event.

The term registry according to FDA guidance to the Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment is defined as “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [(them) to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.” (25).

Through registries, it is possible to evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics (25).

Patient or health care provider surveys can gather information to assess safety signals; knowledge about labelled adverse events, use of product as labelled.

3.1.1. Non-Interventional studies monitoring

The main activity performed during this internship was to monitor two NIS studies GIDEON and XAMOS. After some time I also started providing help for 5 NIS from the Neurology TA.

In Portugal, the MD is responsible for the implementation and conduct of NIS at BHC.

These two studies were from the pharmacoepidemiological type and started at the time of initial marketing authorization, because of questions that remained after review of the premarketing data and to fulfil the post approval commitment to organisations such as the European Medicines Agency (EMA), so they can also be referred as PASS.

GIDEON is a global, prospective NIS of patients with unresectable HCC who are candidates for systemic therapy and for whom the decision has been taken to treat with Sorafenib. Its primary objective of is to evaluate the safety of Sorafenib in patients with unresectable HCC in real-life practice conditions. Secondary objectives are to: evaluate the efficacy [OS, progression-free survival (PFS), time to progression (TTP), response rate and stable disease rate] of Sorafenib in these patients; determine the duration of therapy according to various patient characteristics; evaluate methods of patient evaluation, diagnosis and follow-up; assess comorbidities and their influence on treatment and outcome in real-life practice rather than a controlled clinical trial setting and evaluate the practice patterns of the physicians involved in the care of these patients.

This study is being conducted according to established regulations and recommendations relating to the conduct of NIS; volume 9A of the Rules Governing Medicinal Products in the European Union, Good Clinical Practice and local laws, regulations and organisations (24-26). In Portugal this study has 11 sites which recruited a total of 45 patients. The sites are dispersed throughout continental Portugal (Figure 3) and 39 investigators are involved in it.

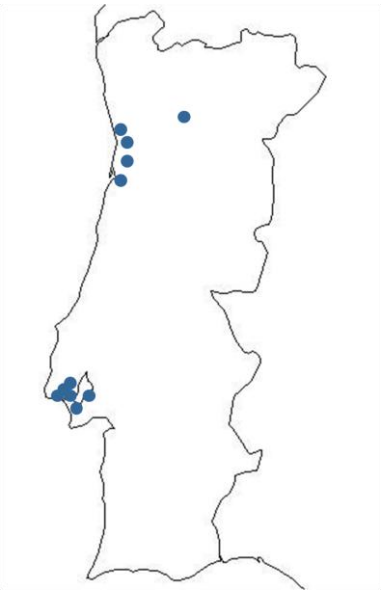


Figure 3. Geographical Location of the Portuguese GIDEON centers

XAMOS is a global, prospective, cohort NIS of Xarelto in patients, who are at least 18 years of age and will undergo elective hip or knee arthroplasty, after the decision for a pharmacologic VTE prophylaxis treatment has been made. two cohorts, one with the drug Xarelto and the other with standard care treatment for VTE prophylaxis were being studied for an observation period of three months were data on bleeding events, symptomatic thromboembolic events and uncommon adverse events (incidence rate between 0.1% and 1%) and mortality causes was collected. Its main goal was to provide additional information to the risk-benefit assessment of the drug (27). 88 patients were recruited by the 2 Portuguese sites for this study.

In Portugal before starting a NIS it is necessary to submit an application to national competent authority, INFARMED and to the National Committee for Data Protection (CNPD).

For these two NIS, there was a written study plan/protocol that although according to law was not obliged to be reviewed was reviewed by the National Ethics Committee for Clinical Research (CEIC).

After obtaining authorization from the competent authorities, these studies also had to be submitted for approval by the administrations and ethics committees of the chosen sites. These entities usually ask for review documents such as:

- Study Protocol;
- Informed Consent;
- Summary of Product Characteristics;
- Investigator Curriculum Vitae;
- Financial Agreement.

During this internship I had the opportunity to prepare the submission package of a new paediatric NIS. The aim of this non-interventional study is to obtain further data on the safety, tolerability, and effectiveness of Betaferon® under daily living conditions in children diagnosed with Relapse Remitting Multiple Sclerosis (RRMS) and being 12 years or older (28). I had to contact with the

investigator and study coordinators in order to gather all the documentation needed for the package. I also had to do a research on the specificities of the submission package for this site, such as a questionnaire that the ethical commission for this hospital demanded and the financial protocol template that this institution required. In order to organize and track all the documents needed for this submission I created a Submission Checklist that would be updated when I had gather each document, When I had all the documents collected and prepared the package I arranged a meeting with the study coordinator, who was responsible for the submission to the ethics committee of studies to be performed on the service she works at and which was chosen to participate in this study.

All the studies only started after a financial and investigational agreement was signed between the administration boards, the principal investigator and BHC. These signed contracts specified the nature of the services to be provided, subject, and if applicable the basis for payment of those services. These contracts also stated the responsibilities for the site, BHC and the investigator.

Any remuneration agreed among the parts was reasonable and reflected the fair market value of the work performed.

For one of the NIS I was monitoring, a centre decided to add elements to their investigational team, so an amendment to the financial protocol had to be written. I participated in this process by helping out collecting the new data needed from the investigators, writing the amendment and submitting it to the hospital administration.

At some points in the internship I also assisted on the process of payments to the sites by accounting which visits needed to be paid and contacting the hospital administrations and financial services to request those invoices. When the payments were performed I also had the task of informing the investigators about it. These payments were always done according to the signed financial agreements.

When a NIS first starts in a hospital, a site initiation visit is usually performed with the investigational team. I participated in one of these visits were the study concept; inclusion and exclusion criteria; enrolment and SAE reporting procedure were explained. The data collection procedure and responsibilities were also discussed.

Since these are two non-interventional studies, the assignment of the patient to a particular therapeutic strategy falls within current practice, therefore the exclusion criteria was the same as the one stated in the local product information and no additional insurance was needed.

Before patients were enrolled in either study and information on them was gathered, they had to sign an informed consent form. The central idea of informed consent forms in NIS is to:

- let know the patients about the purpose of research and the protocol design;
- explain voluntariness status (i.e. participants may withdraw from the NIS at any time without any consequence to their health);
- explain the risks and benefits (29).

One of the main differences between the studies I was monitoring was how the data collection was performed.

GIDEON centres only used electronic data capture (EDC) in the form of an electronic case report form to enter the collected data.

As for XAMOS both electronic case report forms and paper ones were employed. When the centres used paper CRFs, it was necessary for me to collect them and send them via mail to the international organization responsible for database data entry. When I was performing this task I usually did a primary check to see if there was any information missing. The EDC system presented an advantage in this field, because when any field of the CRF was left blank it immediately posted a warning/reminder for the Investigator.

If defined in the monitoring plan or by the global project manager I also had to do free text translations to English for some of the paper CRFs.

When EDC systems were used, queries or data clarifications issued by the data managers were also transmitted electronically in the eCRF.

For the paper CRF sites I usually received periodically data clarification forms by email that I had to make sure that the site received and answered in a timely manner. These answers needed to be sent to international team as soon as possible.

Other important procedure in these NIS was to ensure that all serious adverse events were inserted into the CRFs and were notified to drug safety unit within 24 hours, in order to fulfil the pharmacovigilance regulatory requirements.

During the on the job training both studies ended earlier than expected their recruitment, because of an extraordinary performance worldwide. Consequently not only had all the investigators to be warned about the new deadline for end of the enrolment of new patients but also the hospital administrations. This was made either by email or mail letter that I wrote.

3.1.2. Quality assurance in non-interventional studies

Given that NIS are observational in nature, they can be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Quality assurance tries to overcome these limitations by guaranteeing authenticity, completeness and validity of the data, identifying and resolving deficiencies at an early stage (25, 30).

Quality of a NIS includes the requirements on:

- scientific/professional qualification as well as the personal, technical and spatial equipment of persons/sites involved in the NIS;
- the processes during planning, conducting, analysis and report writing, publication and archiving ;
- the quality of the data and methods for analysing the data.

In BHC there are developed SOP describing the processes during planning, conduct, evaluation and reporting of a non-interventional study, as well as a description of the accompanying quality

measures to achieve a high quality of the data and are part of the overall quality management plan for NIS.

One of these measures is the process of quality review that both GIDEON and XAMOS underwent during this hand-job training.

The aim of these quality reviews was to check whether the study was being conducted in compliance with the approved study protocol as well as that the collected data had been captured accurately and completely and is verifiable from source documents.

The quality reviews performed involved on site data review by an independent clinical research associate(CRA) that carried out source data verification (SDV) on a predefined percentage of the selected centre subjects case report forms (CRF) as defined in the studies specific requirements. Source Data Verification is the comparison of the CRF with the source data that can be found in medical records, laboratory results, among other documents, to ensure the data is accurately captured in the CRF.

These quality reviews also intended to confirm existence of patients, assure that each patient signed an informed consent, and identify systematic errors in the study conduct and documentation.

Before these two quality reviews I had to perform several visits in order to prepare the selected sited for the quality review visit and to explain to the investigators how this process would work.

No major findings or discrepancies were found for either study.

Other quality assurance measure was the monitoring that I performed on a percentage of the recruited patient, has it had been defined in the Data Monitoring Plan of these studies.

Periodical reports and communication with the Global Project Manager through e-mail or teleconferences also allowed to ensure that any emergent issues were rapidly transmitted and when necessary corrected.

3.1.3. Medical Writing and Protocol Development

The medical department responsibles for the Neurology TA came up with an idea for a national/local NIS on therapeutic adherence strategies in patients diagnosed with Multiple Sclerosis treated with Betaferon that would evaluate a strategy involving frequent pharmacist contact to improve therapeutic adherence. I was appointed responsible for writing this NIS protocol.

Non medication adherence has long been recognized as an important limiting factor in the management of chronic diseases such as Multiple Sclerosis and in difficult economic times as the ones we are living today it only gained more importance.

In order to prepare this study and gather specialized opinions/counselling on the study concept and feasibility it was decided to organize a council meeting where the medication adherence subject would be discussed by a group of hospital pharmacist.

I helped out in the preparation of this meeting by performing a bibliographic research on Medication Adherence that would also be used as basis for the development of the study concept and protocol.

For this purpose I searched Pubmed for reports published in the last 5 years using the search terms “medication adherence”, “therapeutic adherence”, “therapeutic compliance”, “medication compliance”, “compliance strategies”, “adherence strategies”, “adherence interventions”, “medication adherence multiple sclerosis” among others. I also performed a more specific search on adherence strategies using pharmacist and on the role of this HCP on adherence.

In order to collect examples of other studies evaluating adherence strategies I also did a search on this topic with special attention on studies involving long term diseases, such as HIV or rheumatoid arthritis.

The results of this research were used on the preparation of three power point presentations presented at the council meeting and on the introduction of the study concept and protocol.

For the council meeting I also prepared a presentation on the study that explained not only the main idea behind it but also the roles of the study members, the study design and timelines. This presentation also had the main questions that we wanted an opinion on from the members of the council meeting such as the recommended frequency of pharmacist contact (see XX).

I also attended the council meeting in which I was responsible for the documentation of all the presentations and opinions on a document that would summarize the main conclusions of the meeting.

This meeting was crucial to clarify some questions that had been raised during the first meetings where the study concept and protocol were discussed.

All the while during this meeting preparation I started writing the protocol and study concept.

This last document, according to the SOP had to be submitted before the protocol, so that the international company representatives could review and approve the implementation and the scientific pertinence of this study. The study concept is constituted by:

- an introduction – where the background and study rational are explained;
- study objectives;
- study design;
- study population – exclusion and inclusion criteria;
- study outcomes;
- data collection;
- data quality.

Opinion on from the International team on this document is still pending, but I am continuing to develop and write the protocol.

Another member of the Medical Department also came up with an idea for a study this time for the cardiology therapeutic area. This NIS would study the treatment preferences of patients with atrial fibrillation being treated with anticoagulants. It was agreed internally that the protocol and concept for this study would be developed by a Clinical Research Organization (CRO). Proposals were

requested in several CROs acting in Portugal and meeting were scheduled to discuss with them the concept and their ideas. I was able to participate in these meetings which allowed me to have contact with another way of developing non-Interventional studies by outsourcing the work.

3.2. Multidisciplinary training

3.2.1. Pharmacovigilance

During the 1960's, 10000 infants in Europe, Australia and Japan were born with phocomelia (a limb reduction congenital anomaly) as the result of exposure in uterus to thalidomide, a medicine marketed as a sedative and used in the treatment of nausea in pregnant women that consequently was banned from the market for this indication. Throughout the experimental phase in rats this reaction was not seen. In the USA this tragedy was averted because the approval of the medicine had been hold given that there were concerns about peripheral neuropathy and of the potential effects of this drug could have on a pregnant woman (31).

This incident brought into attention the importance of drug monitoring systems, detailed testing protocol and of rigorous toxicity testing of pharmaceuticals prior to their marketing authorization.

Since this tragedy much has been done in terms of the pharmacovigilance regulation, development of spontaneous reporting systems, identification of risks associated with medicines and in the minimization measures for said risks. And in the last decades more than 130 pharmaceutical products have been withdrawn on a worldwide basis due to safety alarms (32).

Recently, one of the most publicized cases was the withdraw of rofecoxib (Vioxx®), a nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of rheumatoid arthritis (designed to inhibit selectively cyclooxygenase-2 (COX-2)) after the finding of an increased risk of myocardial infarctions and strokes in patients treated with this medicine (33, 34).

But despite all the efforts adverse drug reactions (ADRs) are still one of the major causes of morbidity and mortality. In the USA, the costs ADRs are estimated to be 1.5-4bilions per year and account approximately for 5.3%of all hospital admissions (35, 36).

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (37).

One of the most important activities in PV is the monitoring of medicines in real life conditions of use to identify previously unrecognized adverse effects or changes in the patterns of adverse effects. This is especially important since the data collected during the pre-marketing phase in clinical trials is often insufficient to create a complete safety profile of the drug since it is limited by factors such as sample size, duration and the conditions are very different from those of clinical practice. The continuous surveillance of the market is also vital to identify rare but serious ADRs, chronic toxicity, drug interactions and specials precautions of use in groups such as children or renal impaired patients that were not previously available.

Both industry and regulators must carry out pharmacovigilance activities since is carried out by both industry and regulators since notification and reporting of suspected ADR arising with the use of medicinal products, by healthcare professionals and consumers, is an essential source of new information (38).

Other central activity in the drug safety field is assessing the benefits and risks of medicinal products to take a decision on what action, if any, is necessary to improve the safe use of the medicinal products. The impact of any action that is taken should also be measured.

It is also in the scope of PV to provide information to the public and healthcare professionals to optimize the safe and effective use of medicines. The Portuguese regulatory authority for instance keeps an online database of all the educational material to consumers and HCP authorized by them (39).

As the Marketing Authorization Holder (MAH), BHC must ensure that it has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.

Portuguese regulations also require a nominated individual in Portugal who has specific legal obligations in respect of pharmacovigilance at a national level. In BHC case it is the Pharmacovigilance Country Head (PVCH), a role taken by the Medical Director.

The pharmacovigilance section of the medical affairs department is also constituted by the Local Drug Safety Manager Deputy (LDSMD) and its back-up.

Another import component in BHC pharmacovigilance system is the ARGUS Central software that allows to insert the ICSR into a database, transmit them to Global Pharmacovigilance (GPV), send it to the regulatory authorities electronically and archive it.

GPV is responsible for world-wide collection, distribution and evaluation of drug safety information, and global management of drug safety issues.

The pharmacovigilance system also has a local emergency phone line to ensure that urgent requests by phone outside working hours (5.00 pm - 08.00 am) are answered by qualified persons without undue delay.

The PVCH is responsible for ensuring that all new collaborators receive training on pharmacovigilance.

PVCH also has to ensure that training on basics in PV and reporting requirements is given at least annually to all collaborators. This is especially important for sales representatives since they have contact with HCP and are often directly informed about ADRs.

All these trainings must be recorded and archived locally for compliance, audit and inspections purposes. The training documentation should include a least of the trainees (with their signatures), the training agenda and a copy of any material presented during the training.

According to directive 2010/84/EU an ADR is defined as a response to a medicinal product which is noxious and unintended. “Response to a medicinal product” in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (this means that a causal relationship cannot be ruled out). It also includes adverse clinical

consequences associated with use of the product outside the terms of the Summary of Product Characteristics (SPC) (17, 40).

A serious adverse reaction or event is described as any adverse event or reaction that:

- results in death;
- is life threatening (i.e. the patient was at risk of death at the time of the reaction);
- requires hospitalization was necessary or prolonged an existing one;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect;
- is considered an important medical event that might not immediately cause one of the above but jeopardised the patient or required additional intervention.

Adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment (23). An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (23).

An unexpected adverse reaction is any reaction which the nature, intensity, consequences and gravity aren't compatible with the SPC) (17, 41).

An unlisted adverse reaction that is one that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). The CCSI contains all relevant safety information contained in the company core data sheet (CCDS) prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification.

CCDS is a document prepared by the MAH that, in addition to safety information, contains material relating to indications, dosing, pharmacology and other information concerning the product.

An individual case safety report (ICSR) is the document providing the most complete information related to the information granted by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time (24). The term ICSR includes unsolicited ("spontaneous") and solicited reports about AE and ADR that may come from the regulatory authorities, HCP or any other source.

A unsolicited communication by a healthcare professional or consumer to a company or regulatory authority that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme is considered a spontaneous report (41).

Other source of unsolicited ICSR is scientific literature, for that reason MAH is expected to regularly screen systematic literature reviews or reference databases. The frequency of the literature search must be of at least every two weeks. At Bayer Portugal this search is performed by the local drug safety manager or its deputy on a weekly base and during this on the job training I had the opportunity to perform it several times.

The literature search consists of screening a Portuguese literature and medical thesis database for the active substances or trade names of the medicinal products for which Bayer is an applicant (42). If the author(s) of a publication identify one of BHC's products as the suspect product of an ADR an ICSR would be created for each identifiable patient. It is important to note that the regulatory clock starts as soon as we found that the case as minimum criteria for reportability. When reporting the individual case, the publication reference would be used as the source. The ICSR would always be accompanied by a copy of the publication and of its translation.

This weekly search would always be documented for compliance purposes.

At BHC a regular screen of Portuguese websites and company email addresses provided on Bayer websites under its responsibility for ADR cases would also be done, since the internet is another one of the sources for unsolicited ICSRs. Training is also provided to the webmasters.

ICSRs may also come from solicited reports from organized data collection systems such as clinical trials, registries and patient support programs, which in the case of BHC is a reality since several patient support programs are implemented in Portugal.

At BHC the following types of case reports are also considered ICSR:

- cases of drug exposure via mother/father with and without adverse events (exposure during conception, pregnancy, childbirth, breastfeeding);
- lack of drug effect medication errors;
- overdose (accidental or intentional);
- drug abuse;
- drug misuse;
- drug dependency;
- pre-existing condition improved (unexpected therapeutic benefits were observed).

When a person outside BHC sends a single case report, the first recipient at the company is usually someone other than the PVCH such as a monitor or sales representative. This person has to forward the information to the local safety within 24 hours of awareness since the clock stars as soon as any person representing BHC has received details of the case.

When the PVCH or its deputy receives the case they must record the clock start date (i.e. the initial receipt date of the case) and make sure that it is present in the source documents. These documents may be AE-form(s), original e-mails, letters, fax cover sheet or unstructured information such as a note from a call.

Spontaneous reports are usually provided in an unstructured way, so the PVCH or its deputy has to initially check whether the incoming information qualifies as a case.

According to the CIOMS definition a case is characterized by fulfilling four criteria (minimum information criteria):

- an identifiable patient;
- the name (INN or trade name) of a (BHC) suspect product or study drug;
- an identifiable reporting source;

- an adverse event .

If there is any information missing or a clarification is needed the PVCH may send a request directly to the reporter or via first recipient. Even if the information is incomplete to avoid any delay in case processing, the case must continue to be reported.

It is also important to verify if the adverse event is associated with a report from a third party about a potential or alleged failure of a product in its quality or suspect counterfeit, i.e. a product technical complaint (PTC). Any information on a PTC is forwarded by the PVCH to the Local Quality Representative (LQR) within one working day. This person is then responsible for the initial assessment and categorization of complaints after receipt; checking if the information is complete and accurate; entering the information into a database and finally handle the response to the customer with help from the PVCH in the medical statement.

The PVCH must enter all PTCs + AE and all follow-up information (e.g. batch-nr.) in the Argus Central Software for further case processing and forward those in addition to the LQR including reference of the AE case ID.

The LQR also has to inform the respective PVCH immediately if a PTC or a suspected counterfeiting incident includes information about a (potential) AE or Lack Of Drug effect (LODE)

The next step is to check if the source documents are in English or if there is the need for translations It is also needed to check if the case may be a duplicates. Then is time to insert the data from the case into the Argus Central software and a local case ID is generated and route it to GPV where it will be processed.

After cases are distributed by GPV via the GPV Database to local PV on day 5 (potential 7-day reports) or day 13 (potential 15-day reports) at the latest the PVCH must decide based on the local legal requirements whether or not to report the reports scheduled for submission via E2B to the authority. If the PVCH decides not to submit a report, the reasoning behind this decision is documented.

All ADRs that are both serious and unexpected independently from the source they come from are subject to expedited reporting. Expedited reporting allows regulators, investigators and other appropriate people aware of new important information on serious reactions.

All serious and unexpected reactions (SUSARs) must be reported to the authorities as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

If a fatal or life-threatening, unexpected ADRs occurs during clinical investigations the Regulatory agencies should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days (40).

The PVCH or the PVCH deputy must check all received reports on a daily basis (40, 41).
During my rotation at PV I had the opportunity to put into practice the procedure of local case receipt and to introduce several cases into the Argus database. Sometimes I was also the first recipient of some serious adverse events that needed to be reported to the local pharmacovigilance as soon as possible so that all the regulatory deadlines were fulfilled.
The PVCH is also responsible to inform investigators and ethics committees involved in BHC-sponsored clinical trials about SUSARs via single case reporting and/or aggregate safety reporting as required by national legislation (43, 44).
According to the Portuguese law, the PVCH also ensures that until the conclusion of a clinical trial ASRs are distributed to ECs and to INFARMED with a list of all Suspected ADRS during this period (43).
For notifications to investigators and ECs, the notifying party retains appropriate documentation (which reports were sent to whom on what date).
The PVCH also tracks the reporting to authorities, investigators, ECs, and any other external contract partners.

3.2.2. Clinical Operations Unit

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions(drugs, cells and other biological products, surgical procedures, radiologic procedures…) to evaluate the effects on health outcomes (45).
Clinical trials (or studies) can be classified according to when the study occurs during clinical development or by their objectives as we can see in Table 2 (46).
Clinical trials should be conducted in accordance with the ethical principles that have their origin in the values outlined by the Nuremberg Code, Belmont Report and Declaration of Helsinki for human subjects research (47-49). Clinical trials must also comply with the International Conference on Harmonisation (ICH) guidelines such as GCP and with the applicable regulatory requirement(s) (50).
BHC is responsible for the launch, management, and financing of several clinical trials.
In 2010-2011 there were six active trials and two NIS in Portugal under the internal management of the Clinical Operations (Clin Ops). There were also five clinical trials being conducted externally by different CROs.
The Clin Ops unit of the medical affairs department is constituted by the country clinical trials manager, three monitors or CRAs (or monitor) and two CTAs.
CTAs main responsibility is to ensure administrative support to Clinical Operations team. They perform submission of Clinical Studies to Ethics Committees (ECs); fill study documents; manage invoices and prepare documentation for sites and investigator's meetings.
CTAs have a liaison role, not only within the Clin Ops team but with the different internal partners they have to contact with on a daily basis such as the Regulatory Affairs Managers (RAM).This

function not only speeds up some of the processes but also assures that GCP's, Portuguese Laws and SOPs are being followed.

Table 2. An example of a clinical trials classification according to its objectives (46)

Type of Study	Objectives of Study
Human Pharmacology	• Assess tolerance • Define/describe PK1and PD2 • Explore drug metabolism and drug interactions • Estimate activity
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation

CRAs are responsible for accompanying the clinical trial and maintaining BHC permanently informed about it, reporting its evolution and ensuring that the trial is conducted an documented properly by verifying the information and data collected.

The monitor is the main liaison between the investigators and the BHC.

Before initiating any clinical trial, BHC has to submit applications to INFARMED, CNPD and CEIC, the competent authorities for clinical studies in Portugal, for review, acceptance and permission to begin the trial in Portugal. The process for submission to INFARMED and CEIC is performed with the help of the Regulatory Affairs department and is discussed in a later section of this on the job training report. Previous to a site initiating a trial it is also necessary to have the administration and ethics committee of the site administration.

BHC acts as the sponsor and according to the ICH E6 its main responsibilities are:

- implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s);

- securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by BHC, and inspection by domestic and foreign regulatory authorities;
- ongoing safety evaluation of the investigational product(s);
- supplying the investigator(s)/institution(s) with the investigational product(s);
- utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports (50).

3.2.2.1. Site Selection Visit (SSV)

According to ICH CGP, BHC is responsible for selecting the investigator(s) and institution(s) where the clinical trial will be conducted. Therefore, a check must be made in order to identify the more suitable investigators through a site selection visit (SSV). This visit is also the first step in relationship building with them (50).

The investigator must be suitably qualified by education, training and clinical experience.

He/she must be able to demonstrate that the site has sufficient resources in terms of qualified staff, adequate facilities, and the potential for recruiting the required number of suitable subjects within the agreed period of time.

When the clinical operations team of the country receives confirmation of participation in one clinical trial a Country Lead Monitor (CLM) is appointed. The CLM then receives study documents such as the study concept, the Investigator's Brochure, a draft or the final version of the protocol, timelines and information on planned costs and timelines. He/she also receives a Site Information Form (SIF) that will be used to collect information from the sites to assess their suitability as an investigational site.

Next an identification team will review all protocol and study details in order to generate a list of potential investigators. This list must illustrate local experience and the investigators past performances by prioritizing them. The identification team members must include the CLM, the country medical expert, the local head of monitoring and study management (LHMStM) and if applicable Marketing colleagues.

Following this process, the CLM or any other monitor delegated by him/her may perform a preliminary contact with the site to see if they are interested in participating in the trial. During this contact the CLM usually does not disclose any confidential information and only discusses the trial in general terms. At this point the CLM may also start completing the SIF.

If the sites are interested the CLM obtains confidentiality agreements and Curriculum Vitaes from potential investigator.

Upon receipt of the confidentiality agreement the CLM may disclose or distribute confidential information like study documents to the potential investigator. The CLM may also send the SIF for

completion by the investigator in order to determine the investigator's suitability and interest for the trial. Sufficient time is given for the investigator to review the protocol and the information provided (50).

The investigator CV must be reviewed in order to verify if he/she is suitably qualified by education, training and clinical experience, therefore it must be up-to-date and no older than one year. To confirm if the site has suitable facilities and patient population for this study the CLM must review the answered SIF.

If the investigator is interested and suitable for the clinical study, the CLM checks if he/she participated in a BHC study in the same therapeutic area (TA) and indication within the last 12 months because if based on adequate past performance, facilities and procedures he may be exempted from the SSV.

The CLM must also report when an investigator is not interested in participating in the trial and if this is due to trial related activities or to operational issues. It is also the CLM responsibility to inform an investigator, if not select.

All these contacts and information have to be filled locally.

After these steps, one of the monitors arranges a SSV with the investigator and its staff with purpose of ensuring that the information on the SIF is accurate and that the investigator really is qualified and has the adequate resources to conduct the trial.

During the SSV the monitor discusses trial details that may include the study population, inclusion/exclusion criteria, study procedures, SAE reporting and study drug information with the potential investigator and staff. The enrolment strategy procedure (enrolment duration, expected recruitment rate…) is also discussed and access to suitable subject population must be confirmed.

The monitor also tries to clarify potential roles and responsibilities of the staff during the study.

The investigator must confirm that he/she know the requirements of ICH-GCP, local laws, regulations and guidelines and will adhere to them.

The rationale of monitoring, audit, regulatory inspection and provision of source data for this purpose should also be discussed. If there will be electronic data capture for this clinical study, it should also be assessed if the site has the conditions for this.

When discussing archiving with the Investigator, the following points must be taken in consideration:

- the Investigator Site File containing the essential documents and source data should be archived for at least 15 years following completion of the trial (as defined in the Protocol);
- the Investigator should inform the Sponsor prior to destruction of the Investigator Site File or source data to confirm it is acceptable for them to be destroyed;
- the Investigator must inform the Sponsor in the event of relocation or transfer of archiving responsibilities.

At the SSV the monitor also confirms if all study and monitoring specific procedures can be performed at the site.

Following the Site Selection Visit, a Site Selection Visit Report (SSVR) must be completed by the

Monitor and a decision must be made regarding the participation of the site.

3.2.2.2. Site Initiation Visit (SIV)

Following site selection the monitor is responsible for ensuring that the site is thoroughly prepared to initiate subject enrolment. Ongoing communication with site staff and other study team members is required to ensure efficient site initiation, many interim site contacts may be required in order to obtain all necessary documentation, to train site staff, and to ensure staff and facilities remain suitable to perform the study following their initial selection. All relevant interim site contacts must be documented in a Contact Report with subsequent action points. Interim site contacts (visit, phone or email) exclude the Site Selection Visit, Site Initiation, Periodic Monitoring Visits or Site Close Out Visit.

Before the Site Initiation Visit the Institutional Review Board and/or its Ethics Committee must have granted permission to start the study at their institution/site, as mentioned earlier.

During the initiation process the monitor has to ensure that all study-related documents (e.g. IB or the final protocol) and supplies needed to conduct the trial are provided to the investigator. The monitor also has to guarantee that all necessary documentation such as financial disclosure forms and investigator agreements were obtained. An important tool that allows the monitor to track progress of mandatory documents sent to and collected from the site on an ongoing basis up until the time of site being notified that they can start enrolment is the Site Document Checklist. The monitor also as to make sure that all study materials such as CRFs, Investigator Site File or study specific equipment have been supplied to the investigator and obtain from he/she a document confirming the receipt.

The monitor also has to complete a Site Contact Details Form with pertinent contact information that will be entered within a clinical trial management system prior to release of study drug and First Patient First Visit (FPFV).

Certain aspects that were already verified during the site selection, such as staff and facilities suitability to perform the study; subject population and enrolment rate have to be checked again to confirm if there were any significant changes.

Other site relevant facilities for the study such as local laboratory or pharmacy have to be contacted in order to confirm if they are aware of their role and responsibilities in the study.

The Monitor must ensure that the site staff is appropriately trained to perform its role within the study prior to FPFV. He/she also have to guarantee that the site staff understand all study procedures and study specific documents. If the staff is working with Electronic Data Capture (EDC) the monitor has to make sure that it performed the appropriate online training and know how to work with the system.

Training may occur at an Investigator Meeting organized by the Study Manager or be performed on site. The monitor may also choose to separate the training into different visits according to the

personnel functions in the study. For example he/she may do a SIV with all the personnel and then one more with only the pharmacy staff. All trainings must be documented in Site Staff Training Record even if an investigator was not present at the SIV but received training at an Investigator Meeting.

The importance and maintenance of the Investigator Site File and the archiving policy for the study documents also have to be explained at SIV. The Investigator Site File is a part of the Trial Master File (TMF) that it is kept at the site and it is the collection of documents retained by the investigator which describe the conduct of the study at the site(s), and collectively demonstrate that the study was performed at the site in compliance with ICH GCP and applicable regulations like the Site Staff Training Record.

The monitor must guarantee that a Site Personnel Identification and Delegation Log has been initiated by the Investigator and has been completed by all relevant personnel. This log must identify the roles of any sub-investigator and the person(s) who will be delegated other study-related tasks; such as CRF/EDC entry. Any changes to this Checklist will need to be reviewed at subsequent monitoring visits.

The investigator and monitor also have to sign a site Source Data Identification checklist that serves to determine the location of the source data. They should also discuss the Permissible Clarifications Form and the investigator has to approve and sign it.

When all requirements have been met for the site to commence enrolment, the Site Initiation Report must be finalized and sent to the site as formal notification that enrolment can begin. The Site Initiation Report will be completed in English. This report should be filed in the Investigator Site File and a copy retained in the Country File.

During my internship I had the opportunity to participate in a SIV. In that visit the monitor did a presentation where she explained the study concept; inclusion and exclusion criteria; enrolment and study specific procedures. She also explained the SAE reporting procedure and times the study staff have to oblige to. Since data collection for this study was going to be made electronically she also explained the system and made sure that the personnel who would be doig the data insertion into the CRF had already received access to it and performed the required training. An overview of the ICH GCP responsibilities was also presented.

After giving time for questions, she started discussing study roles with the study personnel and signing the required forms. She also determined where the source data would be documented from and delivered the Investigator Site File to the Principal Investigator.

In order to prepare for this SIV I read the protocol for the study that was being initiated.

3.2.2.3. Periodic Monitoring visit

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human subjects are protected;
b) The reported trial data are accurate, complete, and verifiable from source documents;

c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s) (43).

Monitoring visits should occur as often as necessary to stay up to date with enrolment. In order to take a better advantage of the periodic monitoring visits (PMV) and to save up the maximum of the investigators' often really busy time, the monitor should thoroughly prepare for the visit by reviewing:

- previous monitoring visit reports (PMVR);
- contact reports;
- drug supply notifications;
- EDC data;
- new safety information (SAE; SUSARs...).

This will allow him/her to identify which study and site specific processes will need to be addressed at the visit. The monitor should also prepare any document that he/she may need to take to the site to update the Investigator Site File (ISF). CTA may prepare these documents for the monitor to archive at the site.

Before a Periodic Monitoring Visit, the monitor should schedule an appointment with the relevant site staff and inform them of the expectations for the visit regarding required actions and access to documentation.

When monitoring one of the subjects the monitor must perform the following activities:

- Review the Informed Consent;
- Review the data and perform Source Data Verification (SDV);
- Check sample handling and study material;
- Review of Study Medication, Accountability Records and Medication Destruction;
- Investigator Site File Maintenance;
- Review of facilities and personnel;
- Conclude the monitoring visit.

These activities may be performed in several periodic monitoring visits.

For each new subject the Informed Consent Form must be reviewed by the monitor to ensure that the applicable approved version was used.

The ICF must be obtained before the subject performed any study specific procedures, so one of the aspects that is key to be verified is its date.

Before signing the ICF, a study team member must explain to the subject (or if necessary to its legal representative) in a clear comprehensive manner the clinical trial objectives, risks, benefits and inconveniences together with the conditions it will be realized in. The subject should also be informed about the trial treatments and randomizations. The subject must be given an ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.

The subject must also be informed that by right he/she may leave the clinical trial at any moment (43). A contact person for questions or more detailed information must be given to the subject. Assure the patient that its moral and physic integrity will be protect together with is personal data and privacy (43, 50). The ICF is a written declaration that these information's where explained to the subject and that he/she agrees to participate in the trial. Both the subject and the investigator who conduct the ICF discussion must sign and date the ICF. This document has to be approved by the institutional ethics committee and has to be revised whenever important new information becomes available that may be relevant to the subject's consent (50).

It is also mandatory that the subject receives one of the signed and dated copies of the ICF.

If a subject is unable to read or if a legally acceptable representative is unable to read, two impartial witnesses should be present during the entire informed consent discussion (43).

After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witnesses should sign and personally date the consent form. By signing the consent form, the witnesses attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

The monitor has to verify if the ICF have been signed and personally dated by all required individuals as defined on the approved ICF and in accordance to local regulatory requirements.

The site personnel signing the IC must have completed the Site Personnel Identification and Delegation Log and have been delegated by the Principal Investigator.

If any discrepancy is found during this review of the ICF or/and of its procedures, those must be documented in the PMVR. These deviations must be one of the priority issues to discuss with site staff and to agree with them what corrective actions have to be taken.

Source Data Verification (SDV) is the comparison of the CRF with Source Data to ensure the data is accurately captured in the CRF. Monitors need to understand the subject data to assure protocol and regulatory compliance along with patient safety and welfare.

The Subject Identification log must be check prior to monitoring any subject to guarantee that all subjects that signed an ICF are listed and if applicable have been enrolled / randomized.

The monitor should review subject's notes and supporting documentation so that he/she understands the overall subject status.

The location of source data needed to be verified must be identified and if any of the required data is missing from the subject's records, the investigator must be reminded to routinely record such data in the records.

When reviewing the CRF the monitor should ensure that all data are legible and/or logical and if applicable are in English. He/She also have to assess compliance with the study protocol and

document in the PMVR any deviations found. The investigator should also document deviations and give an explanation. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator (50).

Discrepancies such as missing data or inconsistencies must be documented by the monitor directly on the EDC system, discussed with the relevant site personnel and where possible solved.

During the PMV the monitor must make sure that data clarifications requests from previous PMVs and if corrections were made directly on the CRF or on Data Clarification Forms (DCF).

One of the most important activities the monitor must perform in any PMV is gurantee that all SAE have been reported and followed-up appropriately.

The investigator must sign off that the data is correct and accurate. If an EDC is used the investigator signature is managed by the system.

At the PMV the monitor guarantee that sufficient materials like central laboratory supplies are available to meet the needs of the site. When applicable, he/she also has to ensure that all material is within its expiry date. Specific instructions for handling of samples/materials/equipment are filled in the ISF. Storage and handling details also have to be documented.

When some of the instructions are filled in another department like the Pharmacy, a cross-reference note should be placed in the relevant section of the ISF.

BHC is required by the regulatory agencies to maintain effective methods of accounting for study medication.

Accountability records should reflect the receipt of medication at site; correct dispensing of medication to study subjects; return of used/unused medication and destruction of unused medication (if applicable).

Such records allow for reconciliation of the study medication (i.e. amount shipped versus used/dispensed/returned/destroyed).

The monitor is expected to ensure that the site performs and documents ongoing study medication accountability. The monitor should verify the accountability documentation on an ongoing basis.

No study medication may be destroyed by the site without prior written agreement by the Sponsor and the site.

If any medication is ready to be destroyed by the site, the monitor has to give permission first for it to be done in accordance with the current local procedures and BHC requirements. A destruction certificate must be retrieved and filled in the ISF. If the site as such capability the medication packages when agreed between them and BHC may also be destroyed there.

It is the responsibility of the Monitor to ensure the adequacy of site facilities, equipment and personnel remain adequate throughout the study period.

If new personnel are joining the study they must be listed in the personnel identification and delegation log. Thus that document should be assessed during the PMV. The monitor also has to ensure any necessary training on study procedures to new or ongoing personnel as required and

document training in the PMVR. He/she must collect new and/or updated documents such as CVs or Financial Certification/Disclosure Forms at the PMV.
Any changes in personnel or facilities have to be documented in the PMVR.
When an EDC system is being used, the monitor must request that the investigator or delegate enters data into the eCRF. Then he/she will lock it and release it to Data Management.
At the end of the PMV, the monitor may review the overall progress of the study with the investigator and other site personnel. If applicable he/she may formulate and agree on action with the investigator where necessary.
The monitor has to document a list of any remaining data discrepancies, outstanding issues and significant findings to be addressed by the site, and leave it on site or forward it to site later.
The monitor must never forget to complete the Site Visit Log and if applicable make an appointment for the next monitoring visit, as appropriate.
Following the PMV a PMVR must be written in English and it should be completed within 2 weeks of the visit. The report should include the date, visit number, site, monitor and investigator(s) identifications. The monitor should summarize what he/she reviewed and any information regarding significant findings. Actions taken or recommended to assure protocol compliance should also be in the report (50). Information on recruitment rate should also be reported.
The PMVR has to be reviewed by the monitor superior and when approved must be filled in the Country File.
The monitor can send a follow-up report of the visit to the Investigator to inform him/she of any pending issues and action points. This report has to be documented in a Contact Report.
During my rotation at the clinical operations I could accompany monitors at various PMV. In addition I had the opportunity to observe how they prepare for the visits and the contacts they had to do with the site personnel. After training with the responsible CTA for that study I also helped preparing all the documentation we had to take to the site to update the TMF. At the PMVs I had the opportunity to see how SDV is done and how the monitors interact with the site personnel. I also had the chance to witness how the accountability procedure goes. After the PMV I was also included in the review process of those PMVR.

3.2.2.4. Site Close Out Visit

Once a site's participation in a clinical study has concluded, close-out procedures should be performed before the clinical study report approval by the means of Site Close Out Visit (COV).
When preparing for the COV the monitor must verify if all required study documents are present in the Country File. In the circumstance that some documents may be missing, he/she must identify those and prepare them to take to the site. I prepared several dossiers with documentation to be used in COV.

The monitor must also identify any other activities that need to be performed at COV, such as collection of equipment drug destruction or storage of samples.

A request should be made to the site for it to have all the documentation available for reconciliation and collection.

During the COV the monitor discusses the reason for the site or study closure with the investigator and summarises conduct of the site with him/her.

At the COV, the monitor must ensure that all Serious Adverse Events have been reported or followed up to BHC and other applicable parties. He/she must also guarantee that all the patient data has been confirmed by the investigator. These data must had been all entry locked so that the site cannot make any changes to it.

Regarding study medication, the monitor is ought to check that all medication has been accounted for. He/She may also check destruction records for the situations where the medication was destroyed at the site. All unused/returned medication must had been collected or if possible arrangements should had been made for it to be destroyed at the site.

In the case that some equipment was delivered to the site to be used for specific study procedures, the monitor has to make arrangements for it to be collected.

It also has to be guaranteed that all biological samples have been shipped to the appropriate location and if all the related documentation was completed.

The monitor is obliged to assure the completeness and consistency of Investigator Site File with the country file, together with obtaining final signatures in documents such as the Site Personnel Identification and Delegation Log, where the investigator should confirm the delegation of responsibilities throughout the course of the study, by signing and dating the log. The monitor should obtain a copy of this log for the Country File, leaving the original in the Investigator Site File.

The site staff is required to sign the Financial Certification/Disclosure Form at the COV and the monitor must ensure that final payments have been made or arrangements were made for payment.

The monitor has to record the future storage location of Investigator Site File and source documents and is required to warn the investigator/site personnel that they have to preserve the records for at least 15 years following completion of the study or until otherwise notified by BHC.

The possibility of future audits/inspections and new data queries should be informed to the relevant site staff.

The investigator should also be told that if he/she leaves the facility or if there is any change in archive responsibilities he/she is obliged to notify BHC of a new contact for access to data.

The Monitor is required to inform other involved site personnel, for example the laboratory or the pharmacy, that the study is complete.

A Site Close Out Visit Report has to be completed in English, within two weeks of the COV.

The monitor or the CTA have to file all documents collected from the site during the COV in the Country File.

If there were any items unresolved after the COV, they must be followed up and documented to the site before the final close out letter is sent. Interim contacts may be performed to inform the site of situations as the sending of the final version of subject data that is suitable for archive or sending confirmations of receipt for returned equipment. These contacts must be filled in the country file.
The monitor also has to inform IRB/IEC and Regulatory Authorities that the study is complete and a copy of these notifications has to be requested for archive purposes.

3.2.3. Regulatory Affairs

The regulatory affairs department is responsible for:

- Clinical trials submissions (working closely with clinical operations);
- Marketing authorization (MA) requests;
- Marketing authorization variations;
- Marketing authorization renewals;
- PSURs;
- Referrals.

This department is made up of six regulatory affairs managers (RAM) that work under the direct management of the technical director. Each RAM is responsible for all the regulatory processes of a predefined number of the company's medicines (either of veterinary or human use). Two of these professionals are also responsible for the clinical trials activities.
In Portugal, the regulation of pharmaceuticals and medical products is the responsibility of the National Authority of Medicines and Health Products (INFARMED), which oversees all technical, scientific, statutory questions related to the marketing of medicines.
Has said earlier in this report, before initiating any clinical trial, BHC has to submit applications to INFARMED, CNPD and CEIC. Regarding these submission processes, the regulatory affairs managers are accountable for gathering, preparing and submitting to INFARMED and CEIC all the necessary documentation that refers to the experimental medicine. RAM also provides all the necessary clinical and pharmaceutical information to the country lead monitor or clinical research associate.
But the first step in requiring for authorization to start a clinical trial is performed earlier by the international team and it consists on obtaining a unique EudraCT number from the EudraCT Community Clinical Trial. This number will identify the protocol for the trial, whether conducted at a single site or at multiple sites in one or more Member States (51).
In Portugal clinical trials submission is regulated by decree-law 46/2004 and INFARMED, IP also emitted a guideline with instructions for the applicants (43, 52).
INFARMED evaluates if the potential benefits for the individual trial subject and society outweigh any eventual foreseeable risks and inconveniences. A trial should be initiated and continued only if the anticipated benefits justify the risks (43, 50).
The submission dossier to this competent authority is composed, among other things, by the:

- A Cover Letter (describing peculiarities of the trial such as trial population);
- EudraCT number confirmation ;
- Investigator Brochure;
- Protocol;
- Complete identification of the sponsor and investigators;
- EudraCT number confirmation;
- Identification of the sponsor (in this case BHC) (in the Clinical trial application form);
- Identification and qualifications of all the team member involved in the clinical trial (in the clinical trial application form);
- Identification of the participating study centres, as well as a declaration of the terms of that participation;
- Investigation Medicinal Product (IMP) Dossier;
- Study specific documents such as the informed consent;
- In the case of a multicenter trial with centres from other member states, identification of the competent authorities and if available the ethics committee opinion, translated to Portuguese;
- Information on all insurances that will cover the BHC's and investigator's responsibilities;
- Information about compensation for patrimonial and non-patrimonial damages, including death chargeable to the clinical trial;
- A copy of the opinion of the Ethics Committee whether the application has been submitted in parallel or in sequence, as soon as it is available ;
- Financial contracts between the centre and BHC;
- Others documents such as the manufacturing authorization or the proof of payment of required tax (43, 52).

INFARMED will deliberate about the authorization request in a period no longer that 60 days after receiving it or 90 days if the study medications is considered genomic therapy, somatic cell therapy or contains genetically modified organisms (43).

Prior to initiating any clinical trial it is also mandatory to receive a favourable opinion from the CEIC. CEIC is an independent organism constituted by healthcare professional and other competent person that will assure that the rights, safety and well-being of the trial subjects are protected (43, 50). The request follows the same structure as the one presented to INFARMED. The opinion will be granted no later than 60 days after the receipt of the request.

Regulatory affairs are also in charge of some post-authorization of the clinical study activities, as for instance:

- Submission of non-substantial and substantial amendments (if they have an impact n the safety of the trial subjects or change the; interpretation of the scientific documents that support the conduct of the trial)

- Notifications on new safety information and on measures taken to protect the subjects against any immediate hazard through the submission of PSURs;
- Notifications of end of study to the CA;
- Submission to the CA of the clinical study report until a year after the end of the study;
- If the trials are suspended, RAM also has to notify the CA.

Prescription and over-the-counter (OTC) drugs have to undergo a registration procedure before starting to be marketed as required by Portugal's Medicine Law of 2006, which incorporated the provisions of the EU pharmaceutical directive 2004/27/EC into national law (44).

Marketing authorization application is also one of the jobs of RA. There are four types of procedures:

- centralised;
- mutual recognition;
- decentralised:
- national.

In 2009 there were a total of 924 MA requests in Portugal, of which 424 were through the National procedure (7).

For the centralized procedure the request is directed to the European Agency of Medicines (EMA) and the after granted the marketing authorization is valid in all European Union member states (53). The scientific evaluation of the application is carried out within the Committee for Medicinal Products for Human Use (CHMP) of the EMA, and a scientific opinion is prepared. Then the opinion is sent to the European Commission which drafts a Decision. Having consulted the Member States through the relevant Standing Committee, the European Commission adopts the Decision and grants a marketing authorisation (53, 54).

The European Community only authorizes through this procedure the following types of medicinal products:

- developed by means of recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; and hybridoma and monoclonal antibody methods;
- containing a new active substance which, was not authorized in the Community, for which the therapeutic indication is the treatment of any of the following diseases:

1. acquired immune deficiency syndrome,
2. cancer,
3. neurodegenerative disorder,
4. diabetes,
5. auto-immune diseases and other immune dysfunctions,
6. viral diseases;

- designated as orphan medicinal products (55).

The decentralised procedure is only possible if the medicinal product does not have a marketing authorization in any of the EU member states. The request for MA may be done in one or more concerned member states (reference and concerned) that approve a draft assessment report, the summary of report, summary of product characteristics (SPC), labelling and package leaflet as proposed by the chosen reference Member State. The applicant must give an assurance that the dossier, including the proposed SPC, labelling and package leaflet, is identical as submitted in all Member States concerned. At the end of the decentralised procedure with a positive agreement, a national marketing authorisation will be issued in the reference Member State and the concerned Member State will comment it.

The mutual recognition procedure is based on existing national decisions in a reference member state that are recognized by all other concerned states. The first step in this procedure is to apply for a MA in one of the member states that will from then on act as the reference member state, that will proceed to the evaluation of the request and if the MA is granted it will be the authorization to use and recognized in other member states for approval (56).

Marketing authorizations are valid for five years. After this period the MAH must apply for a renewal six months in advance of the expiry date of the Marketing Authorization. After the first renewal the authorization is valid for an undetermined time, unless for pharmacovigilance reasons, INFARMED demands a renewal for an additional five year period (44, 57).

Marketing authorization variations are can be classified as:

- Type IA - minor variations have only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation;
- Type IB – minor variation which is neither a Type IA variation nor a Type II variation nor an Extension, that must be notified to the National Competent Authority/EMA by the MAH before implementation, but do not require a formal approval. However, the MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the National Competent Authority/EMA before implementing the change.
- Type II - major variation which is not an extension and which may have a significant impact on the Quality, Safety or Efficacy of a medicinal product.
- Extensions – changes to a Marketing Authorization, that fundamentally alter the terms of this authorization and therefore cannot be granted following a variation procedure. There are three main three main categories of “changes requiring an extension application:
    1. Changes to the active substance(s)
    2. Changes to strength, pharmaceutical form and route of administration (57).

A Transfer of MA is the procedure by which the MA is transferred from the currently approved MAH to a new MAH which is a different person/legal entity. Such a Transfer is needed for example, in the event of a merger/acquisition where the MAH is taken over by another company and ceases to exist as a separate legal entity (57).

PSURs should be submitted electronically and must contain:

- summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization;
- a scientific evaluation of the risk-benefit balance of the medicinal product;
- all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

These reports have to be submitted to the competent authorities immediately upon request or in accordance with the following:

- where a medicinal product has not yet been placed on the market, at least every 6 months following authorization and until the placing on the market;
- where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter (44).

When my job rotation was held on this department I had training in all these procedures with the RAMs.

The regulatory affairs department is also for reviewing in the regulatory perspective all BHC promotional materials, i.e., to confirm if they respect all requirements and have all the elements stated in decree-law176/2006 and on deliberation nr.044/CD/2008 (44, 58). During my training period at RA department I had the opportunity to practice this procedure on several promotional materials both for OTC and prescription-only medicines.

3.2.4. Market Access

The Market Access department main responsibilities are:

- Setting up Market Access Plans;
- Local adaptation of health economic studies;
- Submission and follow up of reimbursement and previous assessment dossiers;
- Preparation of value argument packs adapted to the relevant stakeholders;
- Pricing Management;
- Follow up of the pharmacopolitical environment and its impact.

Before submitting for a public financing request the Portuguese market access department must obtain the maximum ex-factory price (or recommended public sales price) from the Directorate-General for Economic Activities (DGAE). This maximum recommended public sales price in Portugal may not exceed the average price in the reference countries – Spain, France, Italy and Greece.

In Portugal, the overall reimbursement system for Ambulatory Medicines and Portuguese State funding is regulated by Decree-Law 48-A/2010 of 13 May 2010, as amended and the Previous Assessment of Hospital Medicines is regulated by Decree Law 195/2006, 3 October (59, 60).

INFARMED, IP is the authority responsible for the regulation of the prices of reimbursed products which are yearly revised.

Health economic studies play a very important role when requesting for reimbursement or previous assessment, given that with the actual health expenditure growth and the need to control the health budget, it is needed to demonstrate therapeutic added value or economic advantage of the new medicine. All novel active ingredients seeking reimbursement are obliged to present pharmacoeconomic studies that a committee of experts appointed by INFARMED will evaluate. Cost-minimization, cost-effectiveness, cost-utility and cost-benefit analysis using the most common treatment (standard of care) or the most effective treatment are the preferred analysis.

BHC Portugal Market Access has some challenges while adapting core economic models to the Portuguese reality. Since Portugal is a small country, one of the challenges is the fact that there are few national data published so the need exists to previously collect data on national current practices, comparator and costs of interventions.

Other challenge is the long period of time health economic evaluations by INFARMED take when in comparison with other EU countries. The mean time for a decision on a previous assessment for a hospital product with a novel active substance in 2010 was 386 working days (61).

Health Economic Evaluation still is a field with scarce resources and knowhow in Portugal, even though there is a guideline from the public health authority for this type of studies since 1998 (62).

This department is also responsible for advocacy of the company with external stakeholders, such as patient associations, government and industry partners.

During my time at the MA department I had the opportunity to have training on these procedures.

3.2.5. Other activities

This on the job training took place in the 100th anniversary of Bayer in Portugal. To commemorate this milestone, the Medical Department organized a scientific meeting where the macro and micro trends in healthcare, such as the use of robotics, nanomedicines, personalized medicine, e-health, the empowered patient and the hospital of the future. This was a great opportunity to interact and learn from national and international experts such as Dr. Adalberto Campos Fernandes, Dr. Manuel Carrondo, Mautits Butter or Dr. Bertalan Mesko and I was able not only to attend it but also to help in the organization/planning for this event. Dr. Paula Brito e Costa also participated the event and provided a really interesting perspective on the role of the patient.

Other component of this internship was the preparation of the Medical Department report, which is a very important instrument to show to internal and external stakeholders the contribution, and activities that this department undertakes in the company. It also demonstrates the added value it brings to the organization and all of the partnerships it has with important scientific stakeholders such as the Aveiro University; IMM or IBET.

On May 12th I had the opportunity to attend a presentation by Clive R. Wood, PhD from Bayer AG on Innovation in Protein therapeutics where several member of the Portuguese Scientific Field

were present and this topic was discussed together with the role of Bayer on basic research and its partnerships with Portuguese institutes.

4. Discussion

Since this internship was held at a multinational company it gave me the chance to work with people from other countries and to experience how communication is held in projects involving international members. Great English knowledge is crucial in this setting.

The job rotation part of this internship where I had the opportunity to get to know all the different sectors of the company and the functions they perform in BHC was one of the things I valued the most during this period. It also gave me the chance to understand how a company works and an example of management/business system

This internship also allowed me to have more training in the subjects of the different departments and to practice and apply concepts I had acquired throughout my masters course. It gave the opportunity to acquire new notions on areas as medical information and promotion that at the time I had not talked about in the masters.

When I first started with the NIS it was not easy for me to disconnect from the requirements of clinical trials, which from what I have learned demand a lot more specific procedures and documentation. I estranged the fact that some actions like writing a monitoring report were not necessary.

I really appreciated the fact that I could work with two different data capture methods for the NIS. This allowed me to understand not only how to use the electronic method and its advantages over the regular method. Although when using electronic data capture is data transmission and treatment faster and with less probability of error, it is sometimes difficult for the investigators to understand how the system works. Since this were NIS and did not require specific timings for the visits, sometimes there were long periods of time between the logins of the investigator on the system, making them forget how it functioned.

During my internship period I had to do monthly reports which I thought were I great way to summarize the activities I had performed or participated in. The monthly department meetings were also a great learning opportunity, since everyone would trade experiences.

One of the main difficulties during this on the job training was time and priority management, especially when I started accumulating more non-interventional studies and also had to do clinical operations activities.

Sometimes it was difficult to understand the expectations and deadline for some of the activities I had to implement because the “owner” of the project wouldn’t give a detailed deadline (sometimes they would for example tell me “when you have the time could you please do this”) or tell me how he/she were prioritizing it. To overcome this difficulty when someone would assign me a task I started asking and defining very clearly with them the deadline for said task. For the NIS in particular I also implemented spreadsheets with action points for activities planned that I would discuss regularly with the SA responsible for the NIS. Not only was this discussion a great way to define timelines and plans of actions for the studies but also to keep the SA updated on the

activities I had been performing and/or was planning to perform and on the study status (number of patient recruited, centres with more queries, SAEs).

My training on medical writing and the problem based approach of the graduate course I attended also gave me very important skills and methods to search, collect and present information more efficiently.

This hand job training was organised in a way that not only enabled a specific training in non-Interventional studies but also allowed to comprehend how the various departments of a pharmaceutical company work and how they cross functioned. It allow for a transdisciplinar view and application of most of the knowledge learnt from the undergraduate in a real life setting for ten months.

5. Conclusions

The ongoing economic downturn has created challenges for all businesses, and the research based biopharmaceutical sector is no exception.

The R&D process has become more and more complex and costly in recent years, making the already difficult task of developing new medicines harder still.

The investment by the pharmaceutical sector in R&D supports millions of jobs worldwide and invests billions of dollars into several economies. In addition to saving lives, R&D improves quality of life and invigorates the economy.

Medical progress, however cannot be taken for granted since this is a high-risk sector that requires long-term investments. Governments as the Portuguese should encourage these research by creating a regulatory environment through public policies that for example aim to facilitate the approval of clinical studies or increase the human resources on competent authorities so that the responses to applications could be quicker. This would allow a faster access to new and better medicines.

The medical department is a key player in any pharmaceutical company, especially in this period where several regulatory and socioeconomical changes are affecting this sector.

MD must remain the social conscience of the company and keep the interests of the patients in mind. SA will gain even more importance in the pharmaceutical setting since they will be a privileged source of contact with HCPs.

Pharmaceutical biomedicine professionals may provide a very important contribution to any pharmaceutical company, because they have a multidisciplinary view and knowledge of the pharmaceutical market, which makes them a great source of information and communication with several members of the company. These professionals may also perform different roles within a company.

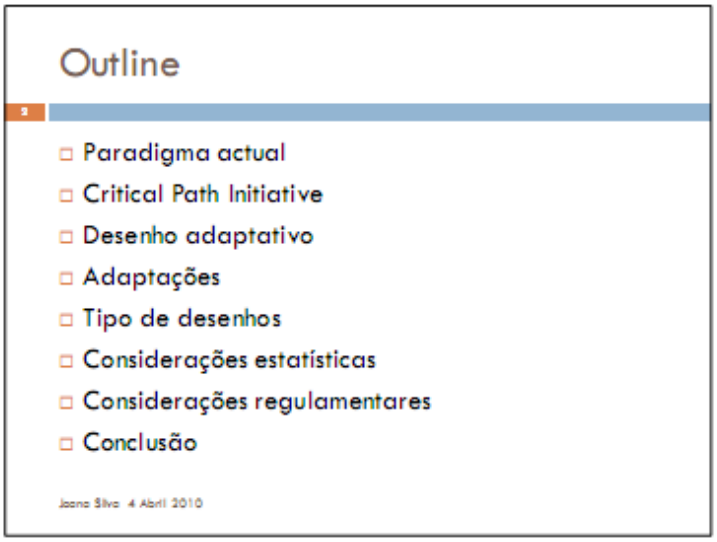
6. References

1. OECD. Health at a Glance: Europe 2010: OECD Publishing.
2. WHO-Europe. WHO Evaluation of the National Health Plan of Portugal (2004–2010). Copenhagen: WHO - EU; 2010. Available from: http://www.euro.who.int/en/where-we-work/member-states/portugal/publications2/who-evaluation-of-the-national-health-plan-of-portugal.
3. PhRMA. Pharmaceutical Industry Profile 2011. Washington, DCApril 2011.
4. John B D. The effect of obesity on health outcomes. Molecular and Cellular Endocrinology. 2010;316(2):104-8.
5. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. The Lancet.374(9696):1196-208.
6. Apifarma. A INDÚSTRIA FARMACÊUTICA EM NÚMEROS - EDIÇÃO 2010: Apifarma2010 May 2010.
7. INFARMED. Estatística do Medicamento 2009. Lisboa: http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES/TEMATICOS/ESTATISTICA_MEDICAMENTO/EstMed-2009.pdf2010 September 2010.
8. OPSS. Relatório de Primavera 2011 Da depressão da crise Para a governação prospectiva da saúde2011.
9. Félix J, Rabiais S, Almeida J. Financiamento público dos medicamentos em Portugal: Acessibilidade aos medicamentos com novas moléculas ou novas indicações terapêuticas: EXIGO2010.
10. DAM. Resultados Operacionais 1.º Semestre 2011: INFARMED, DAM;2011.
11. Arrowsmith J. Phase III and submission failures: 2007–2010. Nature reviews - Drug Discovery. 2011 February 2011;10.
12. Eichler H-G, Aronsson B, Abadie E, Salmonson T. New drug approval success rate in Europe in 2009. Nat Rev Drug Discov. [10.1038/nrd3169]. 2010;9(5):355-6.
13. PhRMA. Drug Discovery and Development - Understanding the R&D process: Phrma; 2007. Available from: http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf.
14. PhRMA. Chart Pack - Biopharmaceuticals in Perspective. PhRMA; [cited 2011]; Available from: http://www.phrma.org/sites/default/files/159/phrma_chart_pack.pdf.
15. L. LaMattina J. The impact of mergers on pharmaceutical R&D. Nature reviews - Drug Discovery. 2011 August;10.
16. Kaitin KI. Obstacles and Opportunities in New Drug Development. Clin Pharmacol Ther. 2008;83(2):210-2.
17. Directive 2010/84/EU of the European Parliament and the Council of the European Union of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use 2010/84/EU (2010).
18. Sehnert C, Doormann B. Bayer Healthcare: The Power of Diversity. Names-Figures-Facts 2011. Leverkusen: Bayer Healthcare AG2011.
19. Marktest G. Marktest apresenta modelo de reputação de marcas. 2010 [updated 21 September 2010; cited 2011]; Available from: http://www.marktest.com/wap/a/n/id~1641.aspx.
20. RCMPHARMA. Top 50 da Indústria Farmacêutica Nacional - Setembro. RCMPHARMA; 2011 [cited 2011 September]; Available from: http://www.rcmpharma.com/industria-farmaceutica/mercado/top-50-da-industria-farmaceutica-nacional-0.
21. Dietlin T, Morris K. Optimizing the Impact of the Medical Affairs Function. Campbell Alliance.
22. EFPIA. EFPIA Code on the promotion of prescription-only medicines to, and with, healthcare professionals: EFPIA; 2011. Available from: http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=11731.
23. 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, (April 2001).
24. Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use, (2008).
25. FDA, CDER, CBER. Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. In: Services USDoHaH, editor.2005.

26. Lencioni R, Marrero J, Venook A, Ye SL, Kudo M. Design and rationale for the non-interventional Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study. International Journal of Clinical Practice. 2010;64(8):1034-41.
27. ClinicalTrials.gov - Xarelto for VTE Prophylaxis After Hip or Knee Arthroplasty (XAMOS). ClinicalTrials.gov; [updated May 26, 2011; cited 2011 May]; Available from: http://clinicaltrials.gov/ct2/show/study/NCT00831714.
28. Clinicaltrials.gov - Study Evaluating Betaferons® Safety and Tolerability In Pediatric Patients With Multiple Sclerosis. NIH; [updated October 24, 2011; cited 2011]; Available from: http://clinicaltrials.gov/ct2/show/NCT00963833?term=betaferon&rank=17.
29. Bernabe RDC, van Thiel GJMW, van Delden JJM, Raaijmakers JAM. Informed consent and phase IV non-interventional drug research. Current Medical Research and Opinion. 2011;27(3):513-8.
30. Theobald K, Capan M, Herbold M, Schinzel S, Hundt F. Quality assurance in non-interventional studies. German Medical Science. 2009;7.
31. Kim JH, Scialli AR. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. Toxicological Sciences. 2011 July 1, 2011;122(1):1-6.
32. Tsintis P, La Mache E. CIOMS and ICH Initiatives in Pharmacovigilance and Risk Management: Overview and Implications. Drug Safety. 2004;27(8):509-17.
33. George A B. Lessons to be learned from the Vioxx debacle. Journal of Nuclear Cardiology.12(1):1-2.
34. Richard H. Vioxx, the implosion of Merck, and aftershocks at the FDA. The Lancet.364(9450):1995-6.
35. Kongkaew C, Noyce PR, Ashcroft DM. Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies. The Annals of Pharmacotherapy. 2008 July/August 2008;42(7):1017-25.
36. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients. JAMA: The Journal of the American Medical Association. 1998 April 15, 1998;279(15):1200-5.
37. WHO. WHO - Pharmacovigilance. World Health Organization; 2011 [cited 2011 June]; Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/.
38. Borg J-J, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and Rationalizing Pharmacovigilance in the EU: Where is Europe Heading to?: A Review of the New EU Legislation on Pharmacovigilance. Drug Safety. 2011;34(3):187-97 10.2165/11586620-000000000-00000.
39. INFARMED. Materiais Educacionais. [cited 2011 September]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/MATERIAIS_EDUCACIONAIS/P_T.
40. EMA. ICH Topic E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting - Note for guidance on clinical safety data management :definitions and standards for expedited reporting. London: European Medicines Agency; 1994.
41. EMA. ICH Topic E2D - Post Approval Safety Data Management London: European Medicines Agency; 2003.
42. Crespo J, Filipe C. Índex Revistas Médicas Portuguesas Online. [cited 2011]; Available from: http://www.indexrmp.com/.
43. Decreto-Lei n.º 46/2004, de 19 de Agosto - Aprova o regime jurídico aplicável à realização de ensaios clínicos com medicamentos de uso humano, 46/2004 (2004).
44. Decreto-Lei n.º 176/2006, de 30 de Agosto Estatuto do Medicamento 176/2006 (2006).
45. WHO. International Clinical Trials Registry Platform. World Health Organization; 2011 [cited 2011]; Available from: http://www.who.int/ictrp/en/.
46. EMA. ICH Topic E8 General considerations for Clinical Trials. London: European Medicines Agency; 1998.
47. OHSR. The Belmont Report Ethical Principles and Guidelines for the protection of human subjects of research. Office of Human Subjects Research [cited 2011 August]; Available from: http://ohsr.od.nih.gov/guidelines/belmont.html.
48. OHSR. Directives for Human Experimentation – Nuremberg Code. Office of Human Subjects Research; [cited 2011 August]; Available from: http://ohsr.od.nih.gov/guidelines/nuremberg.html

49. OHSR. World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Office of Human Subjects Research; [cited 2011 August]; Available from: http://ohsr.od.nih.gov/guidelines/helsinki.html.
50. EMA. ICH Topic E6 (R1) Guideline for Good Clinical Practice. London: European Medicines Agency 2002.
51. Communication from the Commission — 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 (2010).
52. INFARMED. Instruções aos requerentes de Pedido AEC. INFARMED; 2005 [cited 2011]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/INSTRUCOES/instrucoes_0.pdf.
53. EC. Volume 2A - Notice to applicants and regulatory guidelines for medicinal products for human use - Procedures for marketing authorisation - Chapter 4 - Centralised Procedure. Brussels: European Commision; 2006.
54. EC. Volume 2A - Notice to applicants and regulatory guidelines for medicinal products for human use - Procedures for marketing authorisation - Chapter 1 - Marketing Authorisation. Brussels: European Commission; 2005.
55. REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 726/2004 (2004).
56. EC. Volume 2A - Notice to applicants and regulatory guidelines for medicinal products for human use - Procedures for marketing authorisation - Chapter 2 - Mutual Recognition. Brussels: European Commission; 2007.
57. EMA. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. European Medicines Agency; 2011.
58. INFARMED. Deliberação n.º044/CD/2008 - Regulamento sobre os aspectos da publicidade de medicamentos previstos nos artigos 154.°, 162.°, n.o 2, 164.° e 202.°, n.o 1, D, do Decreto-Lei n.o 176/2006, de 30 de Agosto. Lisbon: INFARMED; 2008.
59. Decreto-Lei n.º 48-A/2010, de 13 de Maio Aprova o regime geral das comparticipações do Estado no preço dos medicamentos, altera as regras a que obedece a avaliação prévia de medicamentos para aquisição pelos hospitais do Serviço Nacional de Saúde, procedendo à primeira alteração ao Decreto-Lei n.º 195/2006, de 3 de Outubro, e modifica o regime de formação do preço dos medicamentos sujeitos a receita médica e dos medicamentos não sujeitos a receita médica comparticipados, procedendo à segunda alteração ao Decreto-Lei n.º 65/2007, de 14 de Março, 48-A/2010 (2010).
60. Decreto-Lei n.º 195/2006, de 3 de Outubro Estabelece as regras a que obedece a avaliação prévia, para efeitos da sua aquisição pelos hospitais do Serviço Nacional de Saúde, de medicamentos que devam ser reservados exclusivamente a tratamentos em meio hospitalar, bem como de outros medicamentos sujeitos a receita médica restrita, quando apenas comercializados ao nível hospitalar, 195/2006 (2006).
61. INFARMED. Indicadores de actividade relativos à avaliação de pedidos de avaliação prévia de medicamentos para utilização hospitalar2010.
62. Silva EAd, Pinto CG, Sampaio C, Pereira JA, Drummond M, Trindade R. Orientações metodológicas para estudos de avaliação económica de medicamentos. INFARMED; 1998.

Appendix I - Adaptive Study Designs Presentation



1

Paradigma actual

3

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Critical Path Initiative

4

- Auxiliar os promotores na identificação dos desafios científicos por trás dos problemas de pipeline
- Identificou 6 Desafios de Saúde Pública Prioritários
  - Melhores ferramentas de avaliação – biomarcadores e modelos de doença
  - Simplificar os ensaios clínicos
  - Aproveitar a bioinformática
  - Desenvolvimento de produtos que respondam a necessidades urgentes de saúde pública
  - Populações de risco - pediátrica

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2

Critical Path Initiative

5

- Métodos inovadores de desenhos de estudo, que usem experiências anterior ou dados acumulados
- Encoraja o uso de métodos inovadores de desenhos adaptativos

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Desenho adaptativo

6

- Qualquer desenho que usa dados acumulados para decidir como modificar certos aspectos do estudo enquanto ele continua sem prejudicar a sua validade e integridade.
- Permite adaptações aos procedimentos de estudo ou aos estatísticos depois de iniciado
- Objectivos:
  - identificar eficientemente os benefícios clínicos do tratamento em teste
  - Aumentar a probabilidade de sucesso do desenvolvimento clínico

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Adaptações

7

Prospectivas
- Randomização adaptativa
- Paragem depois de uma análise interina devido a razões de segurança, futilidade ou eficácia
- Re-estimar o tamanho da amostra
- Abandonar os grupos de tratamento inferiores

Concorrentes ou (ad hoc)
- Modificações nos critérios de inclusão/exclusão
- Alteração dos critérios de avaliação, duração do tratamento ou dose/regime
- Alterações nos endpoints de estudo ou na hipótese

Retrospectivas
- Modificações feitas ao plano de análise estatística antes do fecho da base de dados ou unblinding

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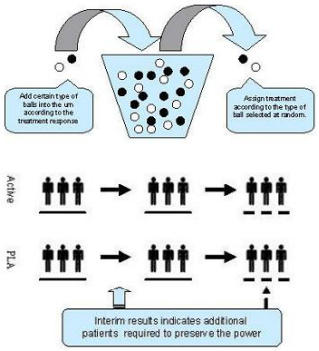
Tipos de estudos adaptativos

8

- Adaptação da randomização
- Grupos sequenciais
- Re-estimação da amostra
- "drop-the-loser"
- Escalonamento da dose



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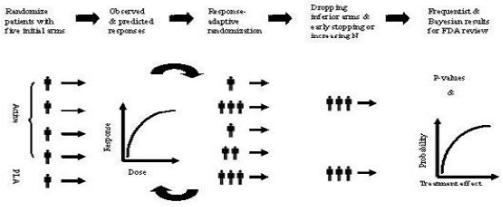
Tipos de estudos adaptativos

9

- Biomarcadores
- "treatment-switching"
- Ensaio de fase II/III
- Múltiplas adaptações



Considerações regulamentares

10

- Que tipo de modificações aos procedimentos do estudo são aceitáveis?
- Quais são os requisitos e standards para a revisão e aprovação dos dados clínicos obtidos de desenhos adaptativos, com níveis diferentes de modificações aos procedimentos de estudo/estatísticos?
- O ensaio clínico tornou-se num completamente diferente depois das alterações?

Considerações estatísticas

11

- Alterações significativas podem introduzir viés/variação na recolha de dados
- Resultar numa mudança na escala do população paciente alvo
- Levar a inconsistência entre as hipóteses a serem testadas e os testes estatísticos correspondentes.

Conclusões

12

Características	Ensaio Convencional	Ensaio Adaptativo
Design	+Rígido	Flexível
Braços de tratamento	2/3 Máximo	Muitos simultaneamente
Modificações	Não são permitidas sem emendas ao protocolo	Pré especificadas são permitidas
Hipóteses	Testa-se a hipótese em consideração	Tenta-se conjugar os dados numa hipótese
Fases	I e II bem definidas	Pode ter um ensaio de fase 2/3 sem barreiras
Análise estatística	Usa métodos frequentistas de rotina	Usa uma abordagem Bayesian

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Conclusões

13

Características	Ensaio Convencional	Ensaio Adaptativo
Organização	Muito simples	+ complicada, requer simulações
Análise Interina	Não é rotina	Feita frequente e rotineiramente
Papel do IDMC	Uma vez por ensaio/quando o ensaio está no fim	Papel proactivo durante todo o ensaio
Perspectiva regulamentar	Completamente apoiados	Ainda espectulatvos

Bibliografia

14

- Chow, S-C; Chang M "Adaptive design methods in clinical trials – a review" Orphanet Journal of Rare diseases2008 , 3:11
- Freidlin, B.; Korn, E. L. "Biomarker-adaptive clinical trial designs" Pharmacogenomics 2010, 11(12)
- Quinlan, J et all "Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development" Clin Trials 2010 7:167
- Cook T, DeMets DL "Review of draft FDA adaptive design guidance" Journal of Biopharmaceutical Statistics, 2010, 20:6, 1132-1142

Appendix II - Compassionate Use Presentation

1

NEWS

As *E. coli* continues to claim lives, new approaches offer hope

On 25 May—just as the deadliest outbreak of *Escherichia coli* on record was beginning to tear through Germany—a team of physicians happened to publish an experimental therapy that could save lives in future outbreaks of this kind. The article described how an antibody therapy called Soliris (eculizumab) had successfully reversed the kidney damage and neurological symptoms seen in three young *E. coli*–infected children suffering from hemolytic-uremic syndrome (HUS), a deadly complication also seen in many victims of the German outbreak (*N. Engl. J. Med.* doi:10.1056/NEJMc1100859, 2011).

Soliris has been on the market since 2007 to treat a rare blood disorder called paroxysmal nocturnal hemoglobinuria, and it costs a

Sprouting up: New treatments target out

product into the hands of physicians there in the immediate future. "We wanted to update them on our current status of development and inquire if there was anything we could do to help," he says.

Antibodies are not the only experimental approach to combating HUS-associated *E. coli*, though. Earlier this year, for example, researchers at the Universities of Buffalo and New Mexico showed that administering zinc-based salts to *E. coli*–infected rabbits lowered

Cancer patients sue for access to experimental drugs

A cancer advocacy group has filed a lawsuit against the US Food and Drug Administration (FDA) in a bid to get experimental cancer drugs into the hands of patients who have exhausted approved treatments.

The Virginia-based Abigail Alliance for Better Access to Developmental Drugs—with mixed support from other advocacy groups—filed the suit on the grounds that current regu-

old daughter, who died of cancer two years ago. Before her death, Abigail Burroughs tried, and failed, to get the experimental drugs Erbitux and Iressa, now touted as wonder drugs for cancer.

Alliance members say that investigational drugs are often the last hope for the terminally ill. But under FDA rules, only a fraction of patients can access them, either by participat-

Research Network. What is that the country has r advocacy, so patient nee

The Alliance is callir changes, including allow ket—on a limited basis strate safety in phase 1 a pursuing accelerated dru minally ill patients who

E. coli crisis opens door for Alexion drug trial

This spring's outbreak of a virulent form of *Escherichia coli* in Germany and France provoked a rapid response from public health authorities and the research community. Not only did the response represent a triumph of global collaboration in rapidly characterizing the Shiga toxin–producing strain but it also prompted an on-the-fly clinical trial of one of the world's most expensive biotech drugs—Alexion's humanized monoclonal antibody Soliris (eculizumab)—previously approved for the rare disease paroxysmal nocturnal hemo-

a new potential indication and they should make a trial out of it," says Schiller.

Soliris suppresses abnormal activation of C5, which damages red blood cells. PNH patients have a mutation in *PIGA*, a gene that encodes glycosyl-phosphatidylinositol, which helps anchor proteins to the membrane. When the mutation is present, cell membranes are more prone to complement-induced damage. As a result, red blood cells break down too early and leak hemoglobin into urine. If enrollment chooses too many red blood cells

Page 3 • Uso Compassivo - Joana Silva •

Bayer HealthCare

Uso Compassivo

- Uso de produto não aprovado (sem AIM)
- Requer que:
  - a situação seja grave
  - haja pelo menos provas preliminares de benefício clínico (ensaios de fase 2…)
  - não haja alternativa terapêutica
  - o fabricante garanta o seu fornecimento até à introdução no mercado
- França, em 2007:
  - + de 20 000 doentes tratados
  - + de 200 produtos

Page 4 • Uso Compassivo - Joana Silva •

Bayer HealthCare

Compassionate use

muitas vezes confunde-se com…

- Off-label Use - Uso de um produto autorizado fora das indicações para que está aprovado

  ≠ Uso de um produto que ainda não foi autorizado.

- Use on a named patient basis de um produto sem AIM ≠ uso compassivo num grupo de doentes

- Importação Individual de produtos autorizados noutros países ≠ uso compassivo num grupo de doentes com essa necessidade e que não necessita de qualquer AIM.

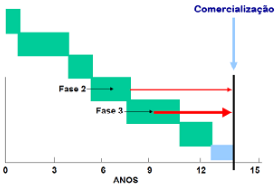
Utilização de Medicamentos sem AIM

Portugal

- **Utilização em ensaios clínicos (e suas extensões de desenvolvimento clínico e de uso compassivo)**
  - Decreto - Lei 46 / 2004 de 19 Agosto
  - Continuidade do tratamento experimental
- **Autorização de utilização especial (AUE)**
  - Decreto-Lei n.º 176/2006, de 30 de Agosto / Deliberação n.º 105/CA/2007
  - Um doente específico sob responsabilidade das Instituições de Saúde
- **Utilização por Protocolo de Acesso Precoce/Alargado/Expandido**
  - Regulamento 726/CE medicamentos no âmbito do procedimento centralizado
  - Um grupo de doentes, por protocolo de utilização terapêutica (e de recolha de dados/informação)

Portugal - Ensaios Clínicos

Decreto - Lei 46/2004



Adapedo de Almeida, L.«Uso compassivo e indução terapêutica», - 10 de Abril de 2006; available from: http://sm.vectweb.pt/media/10/File/Luis__Almeida_Uso_compassivo.pd.

Artº 39º - Fornecimento gratuito e uso compassivo:

"1 - Os medicamentos experimentais e os dispositivos utilizados para a sua administração, bem como os demais medicamentos já autorizados eventualmente necessários à realização de ensaios, são fornecidos gratuitamente pelo promotor.

2 - Após a conclusão do ensaio, o medicamento experimental deve, até à sua introdução no mercado, ser disponibilizado gratuitamente pelo promotor ao participante, desde que o investigador considere indispensável a continuação da sua utilização pelo mesmo e não existam alternativas terapêuticas."

Portugal - AUE

Decreto-Lei n.º 176/2006

Artigo 92.ºAutorização de utilização especial

1. "O INFARMED pode autorizar a utilização em Portugal de **medicamentos não possuidores de qualquer das restantes autorizações** previstas no presente decreto-lei, quando se verifique uma das seguintes condições:

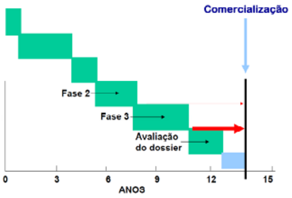
   a)Mediante justificação clínica, sejam considerados imprescindíveis à prevenção, diagnóstico ou tratamento de determinadas patologias;

   b)Sejam necessários para dar resposta à propagação, actual ou potencial, de agentes patogénicos, toxinas, agentes químicos, ou de radiação nuclear, susceptíveis de causar efeitos nocivos;

   c)Em casos excepcionais, sejam adquiridos por **serviço farmacêutico ou farmácia de oficina e dispensados a um doente específico**."

Artigo 93.º Autorização excepcional

1. " O INFARMED pode autorizar, por razões fundamentadas de saúde pública, ainda que abrangidas pelo disposto no artigo anterior, a comercialização de medicamentos que não beneficiem de autorização ou registo válidos em Portugal ou que não tenham sido objecto de um pedido de autorização ou registo válido."



Adaptado de Almeida,L. «Uso compassivo e indução terapêutica», - 10 de Abril de 2006; available from: http://sm.vectweb.pt/media/10File/Luis__Almeida_Uso_compassivo.pd.

Regulamento sobre AUE e AU Excepcional de Medicamentos

Deliberação n.º105/CA/2007

- Autorização a **entidades possuidoras de autorização de aquisição directa de medicamentos com regime de internamento**:
  - Pedidos ao abrigo de AIM
  - Pedidos independentemente de AIM
- Autorização de utilização de lotes de medicamentos em rupturas de stocks e comprovadamente sem alternativa terapêutica
- Utilização especial de medicamentos para resposta a agentes nocivos
- Aquisição por **hospital do SNS para doente específico**
- Aquisição por farmácia de oficina

Regulamento sobre AUE e AU Excepcional de Medicamentos

Deliberação n.º105/CA/2007

- "**Qualquer reacção ou acontecimento adverso decorrente da utilização** de um medicamento para o qual tenha sido concedida uma autorização ao abrigo do presente capítulo deverá, **obrigatoriamente, ser notificada ao INFARMED pela entidade autorizada, sem prejuízo dos deveres de notificação dos profissionais de saúde intervenientes.**"
- "Os requerentes devem, em regra, **apresentar anualmente, durante o mês de Setembro, um pedido único de AUE por medicamento considerado de benefício clínico bem reconhecido, para vigorar no ano seguinte.**"

Portugal

Resumo

Tipo de utilização do medicameto	Legislação aplicável	Responsável/requerente	Objectivo
Uso compassivo por AUE	Decreto-Lei n.º 176/2006, de 30 de Agosto Deliberação n.º 105/CA/2007	Instituição de Saúde	Terapêutico
(Protocolo de) Acesso Alargado	Regulamento 726/CE medicamentos (procedimento centralizado)		Terapêutico/ID
Extensão terapêutica de ensaio para uso compassivo	Lei 46/2004 – artigo 39.º	Promotor de I&D do produto	
Ensaio Clínico	Lei 46/2004		I&D

Adaptado de Beaumont, H. «entidade reguladora, A utilização especial de medicamentos Autorizações especiais e os Protocolos de acesso alargado», - 10 de Abril de 2008; available from: http://sm.vedweb.pt/media10/File/Helena_beaumont_utilizacao_medicamentos.pdf.

EU

Regulamento (CE) 726/CE

Artigo 83.º

"Entende-se por «uso compassivo» a disponibilização de medicamento (…) a **grupo de doentes** que sofram de uma **doença crónica** ou **gravemente debilitante** ou de **uma doença considerada potencialmente mortal** e **não possam ser satisfatoriamente tratados com um medicamento autorizado**."

- O medicamento em causa deve ter sido **sujeito a um pedido de autorização de introdução no mercado**(centralizada) ou **estar a ser submetido a ensaios clínicos**.

EU
Parecer CHMP

- Sempre que se preveja o uso compassivo, o CHMP, após consulta do fabricante ou do requerente, pode dar pareceres sobre:
  - as condições de utilização,
  - as condições de distribuição
  - os doentes visados.
- Estados-Membros têm em conta os pareceres eventualmente existentes.
- Quando for criado um programa de uso compassivo, o requerente zela por que os **doentes participantes tenham igualmente acesso ao novo medicamento durante o período que decorrer entre a autorização e a introdução do medicamento no mercado**.

EU
IV Zanamivir – parecer CHMP

Name of the medicinal product	IV Zanamivir
Company:	F. Hoffmann-La Roche Ltd
Active substance:	Zanamivir
INN:	Zanamivir
Target Population:	Compassionate Use IV zanamivir should be considered only to treat critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic A(H1N1)v infection or infection due to seasonal influenza A or B virus and answering to the following criteria: •Patients not responding to either oral or inhaled authorised antiviral medicinal products, or •Patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or •Patients infected with documented oseltamivir-resistant influenza virus and not suitable for therapy with inhaled zanamivir
Pharmaceutical form(s):	Solution for infusion
Strength(s):	200 mg
Route(s) of administration:	Intravenous
Packaging:	Vials
Package size(s):	1 Vial

USA

- **Compassionate Use**
  - approval for single-patient use of unapproved but efficacious agent.
  - Allows access to promising new therapies following completion of phase II studies for patients not eligible or unable to access phase II or III study.
- **Expanded access**
  - Treatment IND study which allows additional patients to receive new therapies during FDA submission process
  - Use of an investigational drug or biologic to treat a patient with a serious disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition.
  - Minimal eligibility criteria
  - Ongoing collection of efficacy and safety data

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

72 open studies registered

USA

Individual Patient IND under Expanded Access for Non-emergency or Emergency Use

- **Physician Request** - Obtain an unapproved drug for an **individual patient**
- **Manufacturer** of the unapproved drug **must be willing to provide the drug**
- **Written request** must be received by the FDA before shipment of and treatment with the drug may begin
- **Emergency INDs** - request to use the drug may be made via telephone or other rapid means of communication, and authorization to ship and use the drug may be given by the FDA official over the telephone. Shipment of and treatment with the drug may begin prior to FDA's receipt of the written IND submission.

USA
Emergency use authorization

- 2009 H1N1 influenza pandemic
- Public health need for an intravenous agent
- FDA to issue an emergency use authorization (EUA) for the intravenous antiviral peramivir, an unapproved neuraminidase inhibitor (NAI) currently under development.
- Peramivir use was limited to patients for whom other NAI therapy had failed or in whom oral or inhalational drug absorption was believed to be unreliable.

COMMENTARIES

The Emergency Use Authorization of Peramivir IV: A View from the Manufacturer

AS Hollister[1] and WP Sheridan[2]

Bayer
BSP-SOP-704

Supply for **a single patient outside of any clinical trial** of a Bayer drug that is **not marketed or approved for any indication** in the country from which the request originates, or is **not available through normal commercial channels**.

- "Single patient IND", "emergency use of an investigational drug, device or biologic", "Named Prescription", and "Named Patient Supply".
- Does not apply to any investigational compound that has not yet been used in humans.
- Should be discontinued when the product becomes commercially available in that location / region.
- Local legal and regulatory requirements must always be observed.
- Payment for compassionate use drugs will be decided by Bayer based on local / regional laws and regulations.
- For partner / co-development projects the handling of a compassionate use request should be agreed upon within the co-development team / committee.
- The proposed use must not have been declined by Regulatory Authority or by an Ethics Committee / Institutional Review Board. EC/IRB approval must be granted where required.

Bayer
Compassionate use criteria

Sufficient clinical safety and efficacy data **suggest a favorable risk-benefit profile for the proposed use.**

The patient:

- Is suffering from a severely debilitating or life-threatening disease which cannot be treated satisfactorily by an approved drug in the country where the request has originated.
- Has received appropriate standard treatment without success (or no standard treatment exists for the patient's condition) and no satisfactory alternative drug is available.
- Is ineligible or, due to geographical limitations, cannot participate in any ongoing clinical trial, including EAPs, clinical trials or the pivotal trial(s) has completed patient recruitment.

Bayer
Physician / Institution requesting procedures

- Make a written request without solicitation from Bayer.
- Be the treating physician / institution of the patient.
- Confirm that for this patient the potential benefits outweigh the risks based on his/her clinical judgment.
- Be informed of the currently publicly available information on the drug.
- Agree to inform the patient that the drug is not marketed for the proposed use.
- Provided background information about the request and about the patient for whom compassionate use is sought. The minimum required information shall include
  - Unique patient identifier,
  - Relevant medical history and status,
  - Prior treatments including therapies that have failed, have been considered, ruled out or are unavailable,
  - Proposed dose and duration of therapy and indication with description of medical condition for which the drug is requested.

"Compassionate use is controversial because it is a double-edged sword."

Vantagens

- Acesso antecipado a fármacos
- Doentes têm uma sensação de participação no seu tratamento
- Recolha de dados de segurança e de eficácia
- Ajuda ao desenvolvimento de novas indicações

Desvantagens

- Perfil de Segurança do medicamento não está completamente estabelecido
- Custo elevado
- Procedimento de monitorização extenso
- Dados de eficácia recolhidos têm pouco valor para as autoridadesWhereas effi cacy (falta de grupo comparador)
- Dados de segurança são vistos como os dos Ensaios Clínicos
- Doentes têm um estadio mais avançado da doença – performance status e prognóstico pior - certos eventos adversos podem complicar o desenvolvimento e a aprovação do fármaco
- Sobrestima do benefício e Subestima do risco

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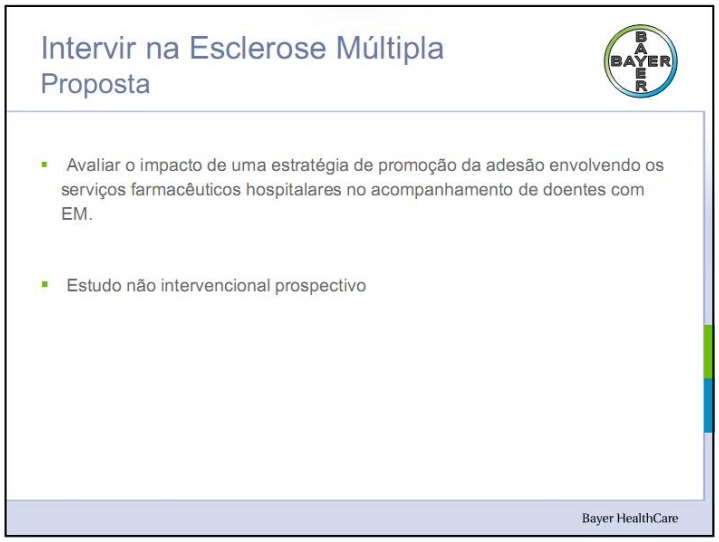
Thank you!

Bibliografia

1. **Regulamento (CE) 726/CE**
2. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007e691
3. ***A entidade reguladora, A utilização especial de medicamentos Autorizações especiais e os Protocolos de acesso alargado, I Jornadas Terapêuticas Acesso a Medicamentos Experimentais em situação de Falência Terapêutica*** **INFARMED 10 de Abril de 2006 Helena Beaumont Departamento de Ensaios Clínicos Direcção de Avaliação Técnico-Científica**
4. **http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AUTORIZACAO_DE_INTRODUCAO_NO_MERCADO/AUTORIZACAO_DE_UTILIZACAO_ESPECIAL**
5. **http://www.infarmed.pt/portal/page/portal/INFARMED/LEGISLACAO/LEGISLACAO_FARMACEUTICA_COMPILADA/TITULO_III/TITULO_III_CAPITULO_I/036-C_Lei_46_2004_1.%AAAIt.pdf**
6. **http://www.infarmed.pt/portal/page/portal/INFARMED/LEGISLACAO/LEGISLACAO_FARMACEUTICA_COMPILADA/TITULO_III/TITULO_III_CAPITULO_I/035-E_DL_176_2006_VF.pdf**
7. **http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AUTORIZACAO_DE_INTRODUCAO_NO_MERCADO/AUTORIZACAO_DE_UTILIZACAO_ESPECIAL/Delib_105CA_2007.pdf**
8. **http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/ACONTECIMENTOS_ADVERSOS**
9. **Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses**
10. http://www.clinicaltrials.gov/ct2/results?term=%22Expanded%20Access%22%20[STUDY-TYPES]&recr=Open

Appendix III – Council Meeting Presentation



1

Intervir na Esclerose Múltipla
Proposta

- Metodologias de optimização/monitorização da Adesão
  - Diário do Doente
  - Contactos telefónicos de *follow-up* com o doente
  - Monitorização da dispensa da medicação
  - Aplicação do *Risk of Drop Out Questionnaire*
  - Educação ao Doente/ Gestão de Expectativas
  - ???

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Intervir na Esclerose Múltipla
Proposta

- Factores que afectam a adesão à terapêutica na Esclerose Múltipla:
  - Dados clínicos e de progressão da doença
  - Dados demográficos e literacia
  - Nível de Incapacidade (EDSS)
  - Avaliação da :
    - Depressão (Hospital Anxiety and Depression Scale)
    - Fadiga (Fatigue Scale for motor and cognitive functions)
    - Qualidade de Vida (EQ-5D)
  - Estratégias previamente instituídas
    - Participação em programas de apoio ao doente
    - Home delivery
    - Auto-injector

????

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2

Intervir na Esclerose Múltipla
População alvo

- Doentes com diagnóstico de SCI ou EMRR em terapêutica com Betaferon®
  - Doente em início de tratamento/ em tratamento?
  - Doente naïve?
  - Estado avançado da doença (EMSP)?

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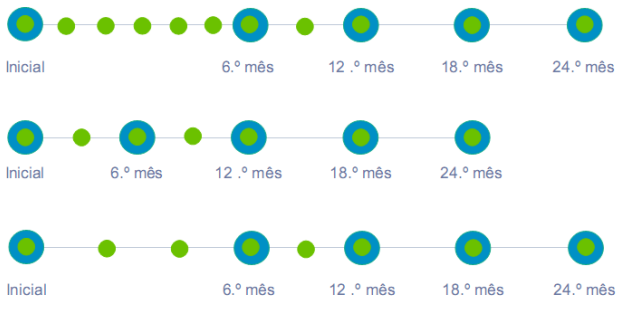
Intervir na Esclerose Múltipla
Periodicidade contactos follow-up?



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Adesão na Esclerose Múltipla
Estudo Prospectivo

Inicial — 6.º mês — 12 .º mês — 18.º mês — 24.º mês

Médico
- Recolha de dados demográficos, clínicos, eficácia e tolerabilidade.

Farmacêutico
- Reunião com o doente no início do estudo – sessão educativa, gestão de expectativas, plano de acompanhamento
- Contactos telefónicos regulares com o doente (periodicidade?)
- Revisão do Diário do Doente

Doente:
- Diário do Doente com registo das injecções regulares
- Questionários

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Próximos Passos

Próximos Passos

- Estudo prospectivo
  - Criação do Protocolo
  - Distribuição do Protocolo para revisão
  - Submissão e Implementação do Estudo
  - Publicações (APFH…)
- Sessão de Esclarecimento
- Submissão de um artigo à Revista Portuguesa de Farmacoterapia

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Thank you!

5