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Relatório Profissional - Keypoint CRO e Boehringer Ingelheim, Portugal

Relatório apresentado à Universidade de Aveiro para o cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor José Luís de Almeida, Professor Convidado da secção Autónoma das Ciências da Saúde e Nélia Lima, Gestora de Estudos Clínicos na KeyPoint CRO.

Professional Report submitted to University of Aveiro to fulfill the requirements for the degree of Master in Pharmaceutical Medicine, held under the guidance of José Luís de Almeida, MD, PhD - Invited Associate Professor and Director of the Masters in Pharmaceutical Medicine at Health Sciences Department, University of Aveiro and Nélia Lima, BSc - Clinical Group Manager at KeyPoint CRO.

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Abstract

Neste relatório, é apresentada a Experiência Profissional entre Fevereiro 2006 e Novembro 2012, como *Clinical Research Associate* (CRA) e *Clinical Project Manager* (CPM) em duas empresas.
Descreve-se os projectos desenvolvidos (Ensaios Clínicos e Estudos Observacionais) como CRA E CPM.

In this report, it is presented the Professional Experience, between February 2006 and November 2012, as Clinical Research Associate (CRA) and Clinical Project Manager (CPM) in two companies.
It is described the projects carried out (Clinical Trials and Non-Interventional Studies) as CRA and CPM.

Report Synopsis

Title:	Professional Experience as Clinical Research Associate and Clinical Project Manager.
Co-ordination:	Nélia Lima, BSc - Clinical Group Manager at KeyPoint CRO Luís Almeida, MD, PhD - Invited Associate Professor and Director of the Masters in Pharmaceutical Medicine at Health Sciences Department, University of Aveiro.
Objective:	The main objective is to present the work developed during these almost seven years and the clinical studies carried out in two companies (Keypoint CRO and Boehringer Ingelheim, Portugal).
Duration:	Since Feb 2006 until Nov 2012
Design:	Since Feb 2006 until Nov 2012 - Clinical Research Associate; Since January 2007 until May 2011 - Clinical Project Manager.
Conclusion:	All acknowledgment acquired along the professional the career was complemented with all the curricular units taught in this Master.

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Abbreviations

ABRASCO	Associação Brasileira de Pós-graduação em Saúde Coletiva
ACCP Guidelines	American College of Chest Physicians Guidelines
AE	Adverse Event
BIAPU	Boletim Informativo da Associação Portuguesa de Urologia
CA	Competent Authority
CEIC	Comissão de Ética para a Investigação Clínica
COPD	Chronic Obstructive Pulmonary Disease
COV	Close-Out Visit
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
EC	Ethics Committee
DMD	Disease Modifying Drugs
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPO	Erythropoietin
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GA	Glatiramer Acetate
GCP	Good Clinical Practice
HMB	Heavy menstrual bleeding
HPV	Human Papillomavirus
ICH	International Conference on Harmonisation

IEA	International Epidemiology Association
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P
IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
LABA	Long acting β_2-agonist
LAMA	Long Acting muscarinic antagonist
MS	Multiple Sclerosis
NSCLC	Non-small-cell lung carcinoma
PD	Pharmacodynamic
PK	Pharmacokinetic
PRCA	Pure red cell aplasia
RMS	Relapsing Multiple Sclerosis
R&D	Research and Development
SAE	Serious Adverse Event
SC	Subcutaneous
SDV	Source Data Verification
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TK	Tyrosine kinase
VTE	venous thromboembolism

Tables and Figures

1. Introduction

1.1. Professional Background

This report is based on a multidisciplinary research work which has been started on February 2006.

During this period I had the opportunity to attempt two different perspectives from the clinical investigation.

I have started my work in clinical research on the field, working together with the researchers and site study team members.

While Clinical Research Associate (CRA), the main concerns to evaluate the data quality, support the site team with the study procedures and identify/manage the difficulties felt internally namely the communication between the different services involved. In parallel, as CRA we must be the bridge between sponsor's obligations (timelines, recruitment goals and timely data entry) and the study team collaboration in achieving all milestones keeping them motivated and engaged.

Later, I had the chance to be part of Management Team as Clinical Project Manager (CPM). In this function, being the main contact between the Sponsor and the CRAs, I started to be responsible for the good studies conduction. This includes but not restricted to, think about the studies and plan them, create all the documents that supports the study conduction (protocol revision, informed consent and definition of data collection variables) and elaborate the monitoring plan as well as the budget accomplishment.

In both functions I felt the need to be part of a team involving CRA, CPM, statistician and medical writer, all with the same main objective – the accurate Medical Writing.

Along this report, it will be detailed the most relevant activities which I have been performed in favor of Clinical Development in Portugal.

1.2. Clinical Development Profile

The total spending on health-related research and development by drug industry has greatly increased in real terms in the last decades[1]. However, the number of innovative new drugs approved each year has not shown a comparable upward trend[1]. Measured by the number of drugs approved per dollar of R&D, the innovative performance of the drug industry appears to have declined.[1]

The traditional R&D model led to stagnation in clinical research due to low productivity, large time to development, high drug failures and these issues involve high costs.

This "productivity gap" has become a problem. The "productivity gap" can be defined as the investment increasing and the number of new medicines decreasing. In our days, with this traditional R&D model it is difficult to find new innovative products.

During the past 10 years, global R&D expenditure in the biopharmaceutical sector has steadily increased, without a corresponding increase in the output of new medicines. The high attrition rate of candidate medicines is a major cause of this declining productivity worldwide. Furthermore, attrition is even more costly because the vast majority of it occurs late in the development cycle. At that stage, major investments have already been made, so the costs of attrition are amplified[2].

The rate of attrition is equivalent to the rate of failure of new medicines. Attrition means discontinuing the development of a biopharmaceutical compound – often for reasons of lack of efficacy or because of potential adverse reactions by patients. It may be the result of a decision by the medicine developer to discontinue development or the failure of the medicine to receive regulatory approval[3].

Improvement, the process of moving a scientific innovation from the laboratory into early clinical studies, is an essential step in modernizing drug development.

In order to support this improvement, and decrease the attrition rate, the European and United States implement in 2004 different initiatives that address the principle causes of delay or bottlenecks in the current biomedical R&D process. In United States, FDA issued the Critical Path Report in 2006[3] and in Europe the IMI created the Strategic Research Agenda (SRA)[4].

In our days, the Drug Discovery Process requires lengthy periods that extent over eight years[5] and enormous cost.

Before the market launch, new drugs undergo a long and a stepwise process, including the efficacy and safety evaluation, investigation and approval of drug applications by regulatory authorities.

In Drug Development, the nonclinical safety assessment for marketing approval of a pharmaceutical usually includes pharmacology, toxicity, toxicokinetic, genotoxicity and reproduction toxicity studies. For drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential must be carried out[6].

This information is used to estimate an initial safe starting dose and dose range for the human trials, and to identify parameters for clinical monitoring for potential adverse effects[6].

In order to quicken and facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R principles (reduce/refine/replace) and reduce the use of other drug development resources, promoting safe, ethical development and availability of new pharmaceuticals it is available a revised ICH guidance M3 (R2). - Current Step 4 Version, dated 11 June 2009[6].

The nonclinical studies can be compared to a bridge, as will link and prepare the First in Man studies.

Human clinical trials are conducted to investigate the efficacy and safety of a pharmaceutical, starting with a relatively low systemic exposure in a small number of subjects. This is followed by clinical trials in which exposure increases by duration and/or size of the exposed patient population[6].

Clinical drug development is often described as consisting of four temporal phases:

Phase I: human pharmacology studies;

Phase II: therapeutic exploratory studies;

Phase III: therapeutic confirmatory studies;

Phase IV: pragmatic studies; post-marketing approval studies.

It is important to recognize that the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases. It is also important to realize that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan typical sequence will not be appropriate or necessary[7].

Phase I starts with the first administration of the investigational drug into humans, and the goal is define PK/PD, identify side effects, tolerability, evaluate drug metabolism and drug interactions based on trials performed in healthy volunteers. The trials can be dose-tolerance studies, single and multiple dose PK and PD studies or drug interactions [7].

These trials are performed in a small number of subjects, and are allowed the subjects payment.

The phase II clinical trials have usually the objective to explore therapeutic efficacy in patients and determine the doses and regimen for Phase III trials[7]. Clinical trials dose-response exploration are performed in this phase.

Usually, the clinical trials in phase II are performed in a large number of patients (400-500 patients) and to evaluate the efficacy minimum dose.

Phase III clinical trials are defined as therapeutic confirmatory studies, as mentioned before. Clinical trials in this phase are the larger than phase I and II clinical trials, where more than 1000 patients can be included.

Comparative studies, randomized parallel dose-response are also designs of clinical trials in this phase[7].

After drug approval the most important is control the drug safety monitoring the pharmocovigilance, and perform additional PK/PD (Phase I) studies if needed.

Phase IV clinical trials are carried out after the marketing authorization and can have the main objective of collection efficacy and safety information. Comparative effectiveness studies can be done.

Complementary to the above mentioned and upon approval of marketing authorization the Sponsor can continue and should study the products at least for pharmacovigilance purpose of the new molecule by implementation of Non-Intervational Studies. These studies are also very useful in pharmacoeconomic evaluations, or even to observe the real compliance and behavior in clinical practice.

Furthermore these studies can be implemented in order to evaluate the incidence/prevalence of a specific pathology allowing the Sponsor to identify needs in the population. This can be valuable to assess the need of new molecules in orphan diseases.

Apart of the development phase, the clinical trials must be planned and implemented according to ethical concerns. The main objective of the investigational project must meet the population needs and respect the rights, safety and subject's wellbeing.

1.3. Ethics Concerns

The World Medical Association's Declaration of Helsinki (1964), introduced, for the first time, ethical principles for physicians in the conduct of human research.

The Drug and Safety regulation had a progress process and was sequentially improved after woes.

During the XIX century, adulterated mislabeled products lead to the Pure Food and Drug Act, in 1906, that introduced quality, purity and labeling standard criteria. This was the first legislative act concerning food and drugs. In 1930 the name Food and Drug Administration (FDA) was implemented in the United States.

The therapeutic disaster with Sulfanilamide elixir (drug responsible for the deaths of more than 100 children) accelerate final approval in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products, as established the need to demonstrate drug safety before the marketing/commercialization.

In 1941, 300 deaths and injuries due to use of sulfathiazole tablets tainted with sedative phenobartial, lead to the development of Good Manufacturing Practice (GMP) by FDA.

The Nazi regime, and the atrocities performed during those years (experiments that were conducted without subject's consent and caused unnecessary pain, suffering and death to these subjects without benefits for them and scientific strength) lead to the Nuremberg Code, in 1948, that introduced for the first time, the concept of inform consent.

The Nuremberg Code is based in ten principles, like:

- Subject participation must be voluntary (inform consent)
- Preview the scientific benefits

- The risk benefit balance should be made, and the benefits must be powerful
- Previous animal testing
- Avoid all unnecessary physical and mental suffering and injury
- No experiment should be conducted where death or disabling injury can occur
- Proper conditions should be made to protect the patient suffering
- Patient freedom to withdraw the experiment
- The experiment should be conducted only by scientifically qualified persons
- The scientist must stop the experiment at any stage if the experiment continuation can result in subject's injury, disability, or death.

Until 1950, few attention was given to adverse events and in 1952, the first book regarding this theme was published - Meyler's Side Effects of Drugs. In 1960, FDA starts to collect the adverse events reporting and initiated a drug monitorization (side effects evaluation) program in the hospitals.

As a result of Thalidomide tragedy, that was responsible for thousands of grossly deformed newborns, in 1962, the Kefauver-Harris Congressional Amendment was created.

This amendment, mention the need/requirement to evidence drug efficacy before approval and evidence of safety before testing in humans, as result thousands of drugs commercialized before 1962, have been withdrawn for the USA market or obligated to change the labeling. In addition, since this date the adverse drug reactions were required to be reported to FDA.

All the above mentioned tragedies and historical context, led to the Helsinki Declaration, as a set of ethical principles for the medical community regarding human experimentation, and supported in the Nuremberg Code, this is the major guideline which have set cornerstones for the ethical conduct of human experimentation.

The Helsinki Declaration created in 1964 and the 8 sequential amendments and updates (performed in 1975, 1983, 1989, 1996, 2000, 2002, 2004 and 2008) were performed in order to improve the guarantee that the rights, safety and well-being of trial subjects are protected.

1.3.1. ICH-GCP

Harmonization of regulatory requirements was pioneered by the European Community, in the 1980s, as the European Union moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible. At the same time there were bilateral discussions between Europe, Japan and the USA on possibilities for harmonization[8].

The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH[8].

At the first ICH Steering Committee meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonization would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorizing new medicinal products[8].

Nowadays, the clinical trials are conducted according the ICH GCP in order to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union, Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

1.3.2. Portugal Legislation

In Portugal there are three national entities responsible for the Clinical Trials evaluation: INFARMED (National CA) that gives authorization, CEIC (National EC) that and provide an ethics opinion according the national law 46/2004, August 19th (which transposes into our national law the Directive 2001/20/EC) and CNPD that is responsible for authorization of personal data processing and collection. This applies to Clinical Trials.

In what concerns to Non-Interventional Studies and in the absence of National Legislation to these studies, there is a standard procedure for ethical evaluation and authorization - Hospital Administration Board and each Hospital' Ethics Committee. For these studies the CNPD authorization is also needed.

2. Rationale

There are a huge number of concerns when a clinical study is being designed and planned.

Guidelines conduct the clinical development, Helsinki Declaration guarantee that the rights, safety and well-being of trial subjects are protected and besides this, ICH GCP defines the responsibilities and expectations of all participants in the conduct of clinical trials.

All these considerations were taken in account along my professional experience. During this report it will be stated the different concerns/responsibilities depending of the function of CRA or CPM in order to assure that all regulations are being met.

There are common points independently of the type or study phase which includes the ethical concerns and regulatory approvals.

However, different obstacles emerged for distinct studies, which may be related with therapeutic area, hospital administration board (that sometimes limit the recruitment period), studies endpoints, recruitment goals and sponsor timelines.

In this report, it will be described the work developed during these almost seven years at KeyPoint CRO and Boehringer Ingelheim – Portugal. Simultaneously, it will be presented the clinical studies carried out and the different responsibilities involved in each study including some of the difficulties encountered in each.

3. Description of the work developed at KeyPoint CRO

In February 2006 I have joined the KeyPoint CRO assuming CRA function. On January 2007 I also assumed the function of CPM. My collaboration in this company finalized on April 2011.

KeyPoint CRO is a small outsourcing service provider. It is a CRO dedicated to the development and implementation of clinical trials, non-interventional, registry and epidemiologic studies, medical writing and health economics.

3.1. Clinical Research Associate

As mentioned in ICH GCP E6, monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, Good Clinical Practice and the applicable regulatory requirements.

As CRA the main responsibilities are:

Prepare Clinical Studies:

- Carry out feasibilities;
- Evaluate facilities and equipment required by Protocol;
- Check investigator's experience and qualifications, availability and experience of trial staff, access to study population and concurrent studies;
- Check pharmacy availability, facilities, storage conditions needed for Investigational Products;
- Prepare, collect and organize all national and international documentation for submission to Competent Authorities, Ethics Committee, CNPD and to Administration Board of each site;
- Prepare Investigator Site File, Pharmacy File and specific logs;
- Collect all the documents needed to the Site Initiation.

Ensure initiation:

- Prepare and organize study supplies to be sent to each site;
- Ensure that all relevant documentation, which was not been collected before, is obtained (e.g. CVs from study team);
- Prepare the Power Point presentation and Perform Site Initiation Visits.

Studies Monitoring:

- Ensure that all studies are being compliant with GCP and national laws;
- Assure the correct and updated archiving of clinical trial' documentation at the site;
- Guarantee the data quality;
- Review CRF for accuracy, completeness and legibility;
- Promote strategies in order to improve the recruitment;
- Verify the Investigational Medicine Product storage conditions and expire dates in a regular basis;
- Perform all tasks planned in the Monitoring Plan in the planned timelines (contacts, visits);
- Assure the regular contact with the sites;
- Participate in teleconferences with international study team (Sponsor);
- Prepare weekly updates to send CPM;
- Perform On Site Monitoring Visits;
- Follow up the queries;
- Follow and support Studies Inspections;
- Perform the monitoring reports in a timely manner;
- Assure the site pharmacovigilance compliance (timely SAE form completion, AE report and follow-up)

Perform Close Out Visits (COV):

- Inform the health authorities, Ethics Committee and investigators about the study termination and/or completion;
- Ensure archiving of all study documentation relating to each site;
- Ensure the return and destruction of drugs/study supplies.

Below, it is represented the number of sites, patients included, recruitment time and therapeutic area per study in order to characterize the clinical studies detailed along this chapter.

Table 1 - Number of sites, number of included patients, recruitment period and therapeutic area per study, as CRA at KeyPoint CRO.

Study	Sites #	Patients #	Recruitment Period (months)	Therapeutic Area
Endorse	9	3.145	1	Medicine
E-Star	9	44	12	Psychiatry
ReNaCaP	43	2.465	3 months per site	Urology/Oncology
Racecadotril	8	165	15	Pediatrics
NABs	5	35 (15cases, 20controls)	24	Neurology
CLEOPATRE	9	2326	9	Gynecology
PRIMS	21	184	43	Nephrology
Advate	2	3	2006 - ongoing	Hematology
EDI09/01	-	-	-	Gynecology
UV2005/01	-	-	-	Urology

3.1.1. Endorse – "*Epidemiologic International Day for the Evaluation of Patients at Risk of Venous Thrombosis in the Acute Hospital Care Setting*"

Rational

The venous thromboembolism (VTE) is a complication that occurs in patients who are hospitalized due to various medical conditions and surgical interventions. In developed countries, the VTE is the most common cause of death which can be avoid. Over the past 30 years, extensive research has shown that patients who have been the target of major surgeries or who are hospitalized for serious medical conditions are more likely to suffer VTE.

Objectives

The main objective was assess the risk of VTE in Patients ≥40 years-old and admitted to a medical ward, or who were ≥18 years-old and admitted in a surgical ward or admitted for a nonsurgical trauma, in accordance with the 2004 ACCP guidelines.

The Secondary objective was to evaluate VTE prophylaxis.

Responsibilities

My principal responsibilities in this study, as CRA, were to support the CPM on SIVs and review patient clinical data including medical history, current medical conditions, type of surgery, initiation and type of VTE prophylaxis verify of the enrolled patient in 5 Hospitals.

Main Results

More than a half of these hospitalized patients in Portugal were deemed at risk of VTE and less than two-thirds of them received appropriate prophylaxis. New strategies are required for implementation of venous thromboprophylaxis in Portuguese hospitals[9].

Personal Perspective

The crucial point for this study was the quick authorities' approvals. Knowing this, the strategy of the Manager Team was to involve the National Coordinator Investigator in order to get faster approvals having proactive meetings with all Hospital Administration Board.

As CRA, this project was a challenging study due to the short period time to achieve the demanding sponsor's objectives.

Due to the short time and the high number of patient s enrolled, while CRA this project demanded the need to identify the most essential data to be collected from the patient medical charts. This task was supported by the training initially provided and the vital investigators support.

In general, this study allowed me to get fluency in obtains data from patient medical records and also showed that the site internal communication is fundamental for the investigation success.

3.1.2. E-Star – *"Electronic-Schizophrenia Treatment Adherence Registry"*

Rational

The schizophrenia is a psychiatric disorder with high treatment costs. The majority of health care costs are associated to hospitalization or institutionalized care.

The use of long-acting, injectable antipsychotics has demonstrated the increase of patient compliance which can reduce the number of relapses and the need of hospitalization.

More information is needed available on the treatment, practice and outcomes potential of long-acting injectable in clinical practice. This type of data is also important to ensure development of accurate economic models of long term cost effectiveness.

Objectives

The main objectives of this Non-Interventional study were:

- Collect clinical outcome data to assess patients' outcomes by existing risk or disease factors, patients' characteristics or previous medication.
- Prospectively assess medication usage patterns, to document clinical efficacy and long-term treatment outcomes of antipsychotics, in a naturalistic setting.
- Collect retrospective data, which allow the evaluation of treatment outcomes with Long-Acting Injectable compared to previous treatments.
- Evaluate reasons for initiating new antipsychotic therapies.

Responsibilities

My principal responsibilities in this study, as CRA, were to perform SIVs, monitoring visits to review patient clinical data and close-out visits.

Main Results

This non-interventional study was implemented in Portugal in consequence of the good results obtained in Spain[10], but in middle of 2007, this study was cancelled in Portugal, by Sponsor decision.

Personal Perspective

In this study the main barrier was training the investigators in Informed Consent obtainment. In this therapeutic area this step seems to be the most constrain process for the recruitment goals.

As particular note, it should be highlight the private clinics involvement. The participation of these sites turned regulatory process simpler.

However, it was identified that most of physicians involved had no previous experience in clinical studies and consequently a lack of ICH-GCP acknowledgment. For this reason, it was provided training to cover this gap.

3.1.3. ReNaCaP – "*Registo Nacional de Cancro da Próstata*"

Rational

The Prostate Cancer is a frequent pathology whose associated mortality and morbidity is a major problem of public health.

In Portugal, it is unknown the prevalence of this pathology although there are estimates of mortality caused by Prostate Cancer.

Objectives

The aim of this study was to determine the prevalence of prostate cancer in Portugal and characterize patients' treatment and progression.

Responsibilities

I began this study as CRA and during that time I performed Source Data Verification (SDV) in prostate cancer patients charts' included in this study (namely date and method of diagnosis, Gleason score, Total PSA score, previous treatment and clinical stage). I also prepared the power point presentation used in SIVs.

After the SIV, it was important to keep the contact with sites in order to motivate the recruitment as this was the main critical point of the study. The site must recruit all the prostate cancer cases identified in the 3 months after SIV, unless the patient refused to participate.

At the end of recruitment a COV was performed on each site.

Main Results

This study was presented by poster in the XVIII World Congress of Epidemiology e VII Brasilian Congress of Epidemiology organized by ABRASCO and IEA, (occurred between 20 to 24 September 2008)[11].

This study shows that the number of prostate cancer patients referenced in each centre in one year is high, revealing the need to invest in screening programs as well as in developing diagnosis strategies and prevalence studies[12].

Personal Perspective

As mentioned before the main critical point in this study was the correct recruitment during 3 months per site to obtain the closer result with the reality in order to meet the study objective.

The great challenge was the close contact with investigators keeping them motivated to engage the study purpose. In other hand, the high number of sites that each monitor was responsible for, conducted to an increased effort. For the success obtained in this study it was essential the constant team motivation.

3.1.4. Racecadotril – "Observational Study to evaluate the therapy standard versus therapy with racecadotril plus therapy standard in children with gastroenteritis evaluated in outpatients"

Rational

The acute gastroenteritis is a common disease in the pediatric population. The dehydration it seems to be the main risk associated with this condition due to loss of water and electrolytes deficit associated with the ingestion and increased secretion bowel.

The oral rehydration therapy is one of the most effective treatments for rehydration in children suffering from acute diarrhea. However this type of treatment has little effect in reducing the number and amount of stools.

This study aims to evaluate the treatment of acute diarrhea with standard therapy versus racecadotril associated with standard therapy according to the practice clinic as an outpatient.

Objectives

The main objective was to evaluate the percentage of children who normalized the number of stools in 48h after start therapy standard versus therapy with racecadotril plus therapy standard.

Responsibilities

In this study the main responsibilities, as CRA, were to perform SIVs, monitoring visits to review patient clinical data, contacts management and COVs.

Main Results

The adoption of therapy that combines racecadotril with oral rehydration may be advantageous compared to standard treatment of acute diarrhea, whereas essentially less need for reuse of emergency services. On clinical signs and symptoms, although the differences in the effect is not statistically significant with respect to the characteristics of diarrhea in itself, the majority of children progressed to complete resolution of the clinical picture in both groups.

No publication is available.

Personal Perspective

Until now, this was the only study that I had been involved in pediatrics population. Similarly to e-Star study, the informed consent obtaining step seems to have been the most constrain process for the recruitment goals. This issue can be related with the study population (children between 3 months to 5 years old).

In addition, this study had a peculiarity which was the phone contacts that should be done with the children' parents 48 hours and 7 days after the initial evaluation. This phone contact was made by a physician from the KeyPoint team. So, being the main contact between the sites and the KeyPoint physician, the big challenge was the opportunity to create strategies for organize all the contacts and follow-up all the different situations (for instance: incorrect or imperceptible phone numbers, parents who did not answer the phone constantly) .

3.1.5. NABs – Case-Control Study for predictive value of neutralizing antibody evaluation as inefficacy biomarkers in INF Beta therapy in patients with multiple sclerosis

Rational

There are insufficient data on the therapeutic management of patients with multiple sclerosis (MS), in the context of ineffective treatment. The determination of NAB as prognostic markers

could be useful in clinical practice habitual, helping in decision-making before the ineffectiveness of treatment with IFN.

Objectives

The main objective of this non-interventional study was to evaluate the predictive value of neutralizing antibody evaluation as inefficacy biomarkers in INF Beta therapy in patients with multiple sclerosis.

Responsibilities

As CRA, I have performed the submission to CNPD and each local Hospital Ethics Committee and Administration Board. After obtain the approvals, the SIV power point was prepared and SIV was carried out.

Due to the recruitment difficulties, close contacts were carried with physicians in order to remember all the eligibility and match criteria. In addition, a huge number of motivation visits were done for the same reason mentioned before and in order to present the study to the most physicians as possible of each sites' Neurology Service with the purpose to increase the recruitment.

Main Results

The results of this study did not show a predictive relationship of antibodies Neutralizing (NAB) as biomarkers of ineffective treatment with INF beta in patients with MS. Further, no other clinical variables were identified that allowed calculating the predictive value for therapeutic failure.

No publications are available.

Personal Perspective

NABs study was my first project involving Neurology Service and with the particularity to be a Case-Control study. As mentioned before the recruitment was very difficult and due to that this study became a hard study. Different strategies were carried out including the performance of several visits with motivation purposes.

3.1.6. CLEOPATRE – "*Prevalence of Human Papillomavirus Infection in Women in Portugal: The CLEOPATRE Portugal Study*"

Rational

Human papillomavirus (HPV) is responsible for a range of diseases, including cervical cancer[13]. In Portugal, as in other countries of Southern Europe, data from population-based prevalence of HPV infection are scarce or even nonexistent. However, the previous studies in our country allow us to estimate an overall prevalence of HPV infection 4-15%, although, due to the different methodologies used for HPV detection is not always the proportions of infection can be comparable. Thus, it becomes crucial to know the reality in Portugal on the distribution of HPV types, especially in younger women (<25 years), in whom the risk of HPV infection is greater.

Objectives

The primary objectives of the CLEOPATRE Portugal study were to estimate the overall and age-stratified prevalence of cervical HPV infection and to assess HPV prevalence and type-specific distribution by cytological results among women aged 18 to 64 years, who reside in mainland Portugal.

Responsibilities

In this study all the responsibilities associated to CRA function were carried out.

I have started this study collaboration with logistics aspects including: lab kits preparation, planning the samples transference from sites to central lab and ensure that the results were delivered to the physicians in a timely manner.

In parallel, all the efforts were done in order to collect the documentation needed for the authorities submission as faster as possible in order to accelerate the study initiation.

In addition, it was given all the support to the sites team in order to collect the paper CRF and solve the queries in a timely manner. SDV was done to all included patients.

Main Results

The overall prevalence of HPV infection in the study was 19.4% (95% confidence interval, 17.8%-21.0%), with the highest prevalence in women aged 18 to 24 years. High-risk HPV types were detected in 76.5% of infections, of which 36.6% involved multiple types. The commonest high-risk

type was HPV-16. At least 1 of the HPV types 6/11/16/18 was detected in 32.6% of infections. The HPV prevalence in normal cytology samples was 16.5%. There was a statistically significant association between high-risk infection and cytological abnormalities ($P < 0.001$)[13].

Personal Perspective

I had a great learning experience with this study. This study had an ambitious recruitment target in a short period and with a lot of sites. Therefore, it was need to think about strategies to support the sites in order to get them autonomous as faster as possible so the CRA team can be able to start other sites.

As CRA, I learned to prioritize visits, issues and concerns. As the recruitment was ended by closing quotas, it was necessary to keep a very close contact with the sites to avoid the inclusions excess per quota.

Due to difficulty expected in this recruitment per quotas, almost all gynecologists' physicians per site were involved. Several of these physicians had no previous experience in clinical studies and consequently a lack of ICH-GCP acknowledgment. For this reason, it was provided training to all of them.

As is foreseeable, it was necessary a huge logistic to manage the time between travels, contacts and office tasks as preparation of weekly updates.

3.1.7. PRIMS – "*Surveillance Study to Estimate the Incidence of Pure Red Blood Cell Aplasia Among Patients With Chronic Kidney Failure (PRIMS)*"

Rational

This study was prepared as part of Mutual Recognition Procedure with EU Regulatory Authorities regarding the reinstatement of the subcutaneous route of administration for EPREX®.

Objectives

The primary objective for the PRIMS registry of subjects with chronic renal failure was to estimate the incidence rate of erythropoietin (EPO) antibody-mediated pure red cell aplasia (PRCA) with subcutaneous (SC) exposure to the polysorbate 80 formulation of EPREX® and to compare this incidence rate to the incidence rate with SC exposure to other currently marketed recombinant

erythropoietin products (epoetin alfa, epoetin beta, darbepoetin alfa) with adjustment for duration of exposure.

This study is registered in Clinical Trials.gov. ClinicalTrials.gov Identifier: NCT00391287.

Responsibilities

In this study, I have started as CRA but in 2009, I was delegated CPM of the study.

As CRA I had the below mentioned responsibilities:

- Feasibility (evaluate the site ability to conduct the study);
- Evaluate facilities and equipment required by Protocol (namely computer and internet);
- Submission this non-interventional study to CNPD and the selected Hospital' Administration Board and local Ethics Committee;
- Site Initiation visits;
- Monitoring Visits (SDV to 100% data and 100% patients enrolled);
- Weekly telephone contacts with sites/investigators (in a beginning phase in order to promote the recruitment and later in order to remember about the patient' quarterly visits);
- Close Out Visits.

Main Results

Not available.

Personal Perspective

This was a very long study taking 5 years, from implementation to close-out. During this time, several changes in Sponsor and CRO's team have hampered the study implementation.

However, the obstacles were overcome and it was possible to achieve the objective set for Portugal.

An interesting detail of this study was the use of e-CRF. In this time the electronic CRF became usual, I learned to monitor e-CRF and raise questions remotely avoiding time spend on the visits.

3.1.8. Advate – *"Antihemophilic Factor (Recombinant) Plasma/Albumin-Free Method (rAHF PFM): A Phase 3/4, Prospective, Controlled, Randomized, Multi-Center Study to Compare the Efficacy and Safety of Continuous Infusion (CI) Versus Intermittent Bolus Infusion (BI) in Subjects With Severe or Moderately Severe Hemophilia A Undergoing Major Orthopedic Surgery"*

Rational

Continuous Infusion was developed as an alternative to Bolus Infusion to reduce the wide variations of FVIII levels and to decrease the quantity of infused FVIII concentrate. The aim was to maintain stable FVIII levels without the deep troughs that usually accompany BI and may place the patient at risk of bleeding. Up to now, a number of studies have been performed that demonstrate that Continuous Infusion is safe and efficacious in terms of providing hemostasis in the peri-and post-operative management of patients with hemophilia A undergoing various surgical procedures.

This study was registered in Clinical trials.gov with identification: NCT00357656.

Objectives

The main objective if this clinical trial is to compare the hemostatic efficacy and safety of continuous infusion versus intermittent bolus infusion in the intra and post-operative setting employing rAHF-PFM in previously treated patients (PTPs) with severe or moderately severe (baseline factor VIII (FVIII) level <= 2% of normal) hemophilia A undergoing unilateral primary total knee replacement.

The primary outcome measure is the comparison of the cumulative packed red blood cell (PRBC) volume in the drainage fluid during 24 hours following surgery in subjects receiving rAHF-PFM by bolus infusion or continuous infusion.

Responsibilities

As CRA, this was my first clinical. My tasks were assure that the recruitment was achieved and verify all data in CRF based on source data (patient chart), included but not restricted to eligibility criteria, treatment and safety aspects.

This study involved several departments. Laboratory, Pharmacy, Pneumology and Orthopedic Department were regularly visited in order to evaluate the lab material and study drug (expire

date and existing stock), evaluate patient compliance, investigational medicine product conditions, support the site on IMP return and perform SDV to all information collected.

In this study, I had the opportunity to perform the first submission to Infarmed, CEIC, CNPD and Hospital Administration Board involving protocol amendments (substantial and non-substantial) as well as investigator brochures updates.

Main Results

Study Ongoing.

Personal Perspective

Besides this study be my first clinical trial it was also the first study in which I had an international manager as principal contact (to clarify questions, update reports, send visit reports, etc.).

With this, I realized the importance of the Investigators Meeting and the CRA attendance on these events. All the doubts raised during the meeting are clarified by the Project Team and in my opinion Investigators have the opportunity to share opinions and know-how.

In addition, I had the opportunity to learn more about the issues related IMP that must be evaluated in a regular basis including its conditions, expiration dates and compliances.

All sites revealed motivation and interest. However, the recruitment became underwhelming. Strategies to improve it were thought together with site teams and the recruitment was extended and is still ongoing.

All the SOPs were from other international company and the training were carried out as soon as new versions became available.

This contributed to better acknowledgment about clinical trials and drug development.

3.1.9. EDI09/01 – *"A Multicentre, Double-blind, Placebo-controlled, Parallel Group Study Effect of Oral Etamsylate (Dicynone®) in Patients with Menorrhagia"*

Rational

Menorrhagia, defined as excessive menstrual blood loss of greater than 80 mL per period lasting longer than 7 days, has a significant impact on many women's lives. Menorrhagia is the most common cause of anaemia in premenopausal women. Patients who do not respond to medical therapy may require surgical intervention to control the menorrhagia.

Alternative effective treatments to hysterectomy are available for these women with HMB, particularly for those who have a normal uterus and no significant pathology, with norethisterone, non-steroidal anti-inflammatory drugs (NSAIDs) like mefenamic acid and antifibrinolytic drugs like tranexamic acid.

Etamsylate (Dicynone®, Dicynene®) is a non-hormonal synthetic antihaemorrhagic agent, which has its point of impact on the first stage of haemostasis that appears as a therapeutic alternative.

Objectives

This study was designed with the main objective of assess the effect of etamsylate when compared with placebo on the reduction of menstrual blood loss in patients with menorrhagia.

Responsibilities

In this clinical trial, my responsibilities were restricted to study start-up activities. So, I was responsible for feasibilities and physicians' selection, investigators experience evaluation, and all the issues related to Clinical Trial preparation, detailed in CRA function responsibilities, as facilities evaluation and existence of equipment required by Protocol, check investigator's experience and qualifications, availability and experience of trial staff, access to study population and concurrent studies.

In addition, I was also responsible to identify the documentation needed for Infarmed, CEIC, CNPD and to Administration Board submission, prepare the submissions and maintain a close contact with hospitals in order to get a fast approval.

Main Results

This study was internationally cancelled.

Personal Perspective

This clinical trial allowed me to gain experience in the clinical trial submissions preparation.

3.1.10. UV2005/01 – *"Multicentre, Randomised, Double-Blind, Placebo-controlled Clinical Study To Assess The Efficacy And Safety Of Uro-Vaxom® In Chronic Prostatitis And Chronic Pelvic Pain Syndrome (CP/CPPS)"*

Rational

The rationale for performing the present study is to assess the efficacy and safety of Uro-Vaxom® in patients suffering from chronic prostatitis or chronic pelvic pain syndrome. The use of a placebo is justified as all patients will be allowed to take the standard treatments including antibiotics as concomitant medications during the study in cases of acute pain in pelvic region; this being consistent with Helsinki declaration.

Objectives

The main objectives of this clinical trial were the evaluation of the efficacy of Uro-Vaxom® in chronic prostatitis/CPPS and clinical safety.

Responsibilities

The responsibilities taken in this study are very similar to the above mentioned in EDI09/01 study, as in this study no SIVs were done.

Main Results

This study did not started in Portugal due to the long period of Hospital Ethics Committee and Administration Board evaluation and approvals. After the approval the recruitment period was finished.

Personal Perspective

This training in regulatory submissions was a key to feel comfortable in all the further submissions. This clinical trial was also interesting because it allowed me to get back into contact with physicians who were part of the ReNaCaP study.

3.2. Clinical Project Manager

As CPM I was responsible for the following tasks:

- Propose sites, Principal Investigator and the National Coordinator;
- Ensure the management of allocated projects and CRAs for which is responsible
- Assure the management of the local clinical trial' submission and approval processes (regulatory authorities and Hospital Administration Board);
- Assure the correct submission of the clinical trial' amendments (regulatory authorities and Hospital Administration Board);
- Adapting the international trial documents according to the national laws and requirements;
- Hospital's contracts preparation and negotiation;
- Ensure that SOPs, guidelines and National Law are followed throughout all the study preparation by all the parties;
- Ensure the accomplishment of the national timelines;
- Verify the resources needs for the local study conduction;
- Ensure the adequate training of all trial team, including the investigators;
- Prepares and conduct, together with the CRA, the SIV.
- Prepare and coordinate the national investigator's meetings;
- Keep the trial costs within the approved budget;
- Ensure that the national recruitment runs according to the planned and implements corrective measures to improve it, if necessary;
- Assure accomplishment of pharmacovigilance procedures related with the trial;
- Ensure the management of the study close-out timelines;
- Assure the notification to the regulatory authorities, investigators and Hospital Administration Board upon the study closure;
- Team Management (conflicts, workload, costs);
- Identify and prevent difficulties/obstacles in study progress (come up with proactive ideas);
- Evaluate the CRAs performance;
- Prepare and perform co-monitoring visits;
- Prepare the monitoring plan;
- Supervise the timelines achievement;
- Proactive communication with international Study Manager about study status;
- Support the Sponsor on Study Protocol preparation;

- Writes and prepares the essential documents for study conduct (informed consent, CRF, specific logs, etc);
- Revise all the study documentation;
- Order the necessary material for study conduct (study drug and remain material, ex: lab material);
- Technical and scientific guidance;

Below, it is represented the number of sites, patients included, recruitment time and therapeutic area per study in order to characterize the clinical studies detailed along this chapter.

Table 2 - Number of sites, number of included patients, recruitment period and therapeutic area per study, as CPM at KeyPoint CRO.

Study	Sites #	Patients #	Recruitment Period (months)	Therapeutic Area
COPTIMIZE	9	21	24	Neurology
IMAGINE	200	2951	12	Gyneacology
CLEOPATRE II	7	646	9	Gyneacology
ÉVORA	8	15	17	Oncology
CREDIT	16	166	15	Endocrinology
INSPIRE-ME-IAA	12	186	19	Endocrinology

3.2.1. COPTIMIZE – *"A two year observational, non-interventional, global internet based survey of subjects diagnosed with RMS who were previously switched from any DMD to GA"*

Rational

Making therapeutic decisions with no clear criteria that define subjects their current therapy, with no scientific guidelines for the proper time to switch medications and so forth have made therapeutic decisions much more complex. Even data describing the current situation in terms of agreed upon definition of failing therapy on one hand and therapeutic algorithms for failing subjects on the other are scarce and not in agreement by various key opinion leaders. Still multiple sclerosis is a complicated chronic disease and physicians do switch therapy.

For this reason the study aims at gaining more information on the faith of multiple sclerosis subjects experiencing difficulties on Disease Modifying Drugs (DMD) therapy.

Objectives

Assess the disease course of subjects switched from one disease modifying therapy class (interferon) to another (Glatiramer Acetate - GA) as measured by: Annual Relapse Rate (ARR) before and after the switch;

Rate of deterioration as measured by mean Expanded Disability Status Scale (EDSS) /mobility score in the last year prior to the switch and following the switch to GA

Responsibilities

In this study I coordinated all the study implementation, including:

The responsibility do adapt, write and prepare the essential documentation, as the informed consent and specific logs. I also prepare the template of Investigator Site File.

Identify and select the Investigators and as I have worked as CRA in other studies involving the same therapeutic area (NABs study) it was easier to evaluate the investigator's experience and qualifications, availability and experience of trial staff as most of the Investigators were known.

In parallel, I have followed the authority submissions (CNPD and each Administration Board/local Hospital Ethics Committee). I also prepared the Hospital' contracts, based on each Hospital template and in the values defined by Sponsor.

After obtain the approvals, the SIVs were prepared and conducted together with the CRA.

Due to the recruitment difficulties, timelines were successively evaluated and a proactive and frequency communication was established with Sponsor about study status, in order to define new National timelines. This situation led to subsequent costs evaluations.

Main Results

Study Ongoing

Personal Perspectives

This study conducted to a straight relationship with the Sponsor. Weekly study status was sent to Sponsor that was discussed in the frequent teleconference.

Due to the recruitment difficulties several strategies were defined and evaluated in a continuously manner. As needed, new strategies were discussed and identify.

This study was frequently discussed in the internal KeyPoint meetings as it was required the involvement of different people in order to think about strategies to improve the recruitment.

Some monitoring visits were conducted together with CRA in order to motivate and identify possible obstacles at each site.

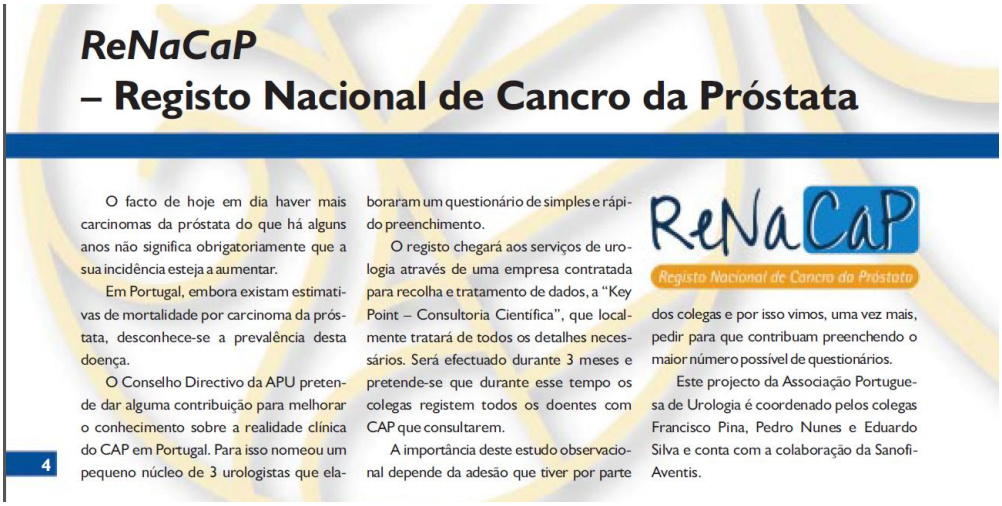
3.2.2. ReNaCaP – "*Registo Nacional de Cancro da Próstata; Prostate Cancer National Registry*"

Responsibilities

In the beginning of 2007, I was designated Project Manager of this study. I was also involved in the final recruitment, motivating the CRA team in order to achieve the 2.500 patients.

In order to advertise all the urologist physicians to ReNaCap study, it was thought with APU this study publicity. This was done in the *Boletim Informativo da Associação Portuguesa de Urologia* (BIAPU), as presented below (Fig. 1).

Figure 1 – ReNaCaP study publicity on Boletim Informativo da Associação Portuguesa de Urologia (BIAPU), Year VII, Num. 2/3, April/September 2007



ReNaCaP
– Registo Nacional de Cancro da Próstata

O facto de hoje em dia haver mais carcinomas da próstata do que há alguns anos não significa obrigatoriamente que a sua incidência esteja a aumentar.

Em Portugal, embora existam estimativas de mortalidade por carcinoma da próstata, desconhece-se a prevalência desta doença.

O Conselho Directivo da APU pretende dar alguma contribuição para melhorar o conhecimento sobre a realidade clínica do CAP em Portugal. Para isso nomeou um pequeno núcleo de 3 urologistas que elaboraram um questionário de simples e rápido preenchimento.

O registo chegará aos serviços de urologia através de uma empresa contratada para recolha e tratamento de dados, a "Key Point – Consultoria Científica", que localmente tratará de todos os detalhes necessários. Será efectuado durante 3 meses e pretende-se que durante esse tempo os colegas registem todos os doentes com CAP que consultarem.

A importância deste estudo observacional depende da adesão que tiver por parte dos colegas e por isso vimos, uma vez mais, pedir para que contribuam preenchendo o maior número possível de questionários.

ReNaCaP
Registo Nacional de Cancro da Próstata

Este projecto da Associação Portuguesa de Urologia é coordenado pelos colegas Francisco Pina, Pedro Nunes e Eduardo Silva e conta com a colaboração da Sanofi-Aventis.

4

After the recruitment phase, I was involved in close-out preparation in order to ensure the management of this task within the timelines.

I also had the responsibility to inform all Hospital Administration Board and investigators about the study closure. All the investigators were also congratulated about the excellent recruitment.

Personal Perspectives

The success of this study as demonstrated by the recruitment obtained was just possible due to the commitment shown by the Sponsor and members of Steering Committee.

It was a gratifying and pleasing work, as I had the opportunity to start in the field and evaluate the main difficulties and then be on the other side supporting the CRAs with new action plans.

3.2.3. IMAGINE – *"Avaliação do IMpacto de um programa de InformAção pelos GINEcologistas, na contracepção hormonal combinada, em Portugal"*

Rational

Supply the wife of an accurate and understandable information about the different contraceptive methods available and their characteristics contributes in a way relevant to the optimization of contraceptive choice, improving its adhesion to the chosen method. Health information provided by doctors to women at the time of the choice of contraceptive method may improve adherence and optimize the adequacy of contraceptive regimen to the needs and lifestyles of each women.

Objectives

Evaluate the choice of the woman, after information and explanation of the three types of methods available in the market for combined hormonal contraception.

Responsibilities

When the study was planned, my principal responsibility was thought about the essential documents for study conduct, including informed consent, CRF and specific logs. The print of the study materials was also my concern.

This study was submitted to all authorities needed (namely CNPD and Hospitals Administration Board). However, in this study, private clinics were involved, which turned regulatory process simpler.

The recruitment target of 3.000 women involving approximately 200 sites was the objective initially defined. For this reason, a team of 4/5 CRAs was designated. The great challenge was then to keep the close contact with CRAs (regular meetings) in order to evaluate the weekly contacts with investigators. In this contacts CRA evaluate the status recruitment per site and the expected recruitment during the next week. This was essential to ensure that the national recruitment ran according to the planned.

I also had a colleague that supported me in with the Sponsor contact, supports the team motivation to engage the study purpose and to implement corrective measures implementation in order to improve the recruitment.

Main Results

The implementation of a counseling program significantly affected contraceptive choices leading in a number of cases to the selection of alternatives better suited to women's lifestyle. Age and educational level are socio-demographic factors which play an important role[14].

Personal Perspectives

Similarly to ReNaCaP study, the great challenge was due to the high number of sites that each monitor was responsible for, which conducted to an increased effort. For the success obtained in this study it was essential the constant team motivation.

Periodic team meetings, definition of different recruitment s and Investigators contacts strategies, management of the budget and Investigators payments were some of my biggest challenge in this study,

Nevertheless, it was a pleasure to be included in this study team and I have proud to be part of such big study which had a great impact in scientific population.

3.2.4. CLEOPATRE – "*Prevalence of HPV Infection in Women in Portugal: The CLEOPATRE Portugal Study*"

Responsibilities

The main responsibilities as CPM in this study were:

- National investigator's meetings preparation together with Sponsor and CLEOPATRE Portugal Study Group;
- Evaluate in a monthly frequency, the trial costs within the approved budget;
- Weekly evaluation of, the planned national recruitment together with sponsor;
- Definition, with the Sponsor, of corrective actions implementation to improve the recruitment;
- Team Management (conflicts, workload, costs);
- Identify and prevent difficulties/obstacles in study progress (come up with proactive ideas);
- Prepare and perform co-monitoring visits;
- Prepare the monitoring plan;
- Evaluate the CRAs performance;
- Ensure the management of the study close-out timelines;
- Notify the investigators and Hospital Administration Board about the study closure;
- Preparation of specific kits for the study.

Rational and Objective described at point 3.1.6.

Personal Perspectives

All the physicians involved were engaged with this project. It was created a great expectation with this study results as it was the first study in Portugal to evaluate the epidemiology of this disease.

So, I have learned that work with a motivated team (physicians, Sponsor and CRO team) makes all studies possible even all those that seem impossible (like this one, 2.326 women included in 8 sites, during 9 months per aging quotas).

Demanding contacts periodicity with the Sponsor was established which conducted to the huge time consumption and in some situations to stress within the team. Nevertheless, at the end this became to be an important tool and conduct probably to the success of the study as all the

difficulties and problems were discussed in a timely manner involving the Sponsor to all the decisions and issues.

To summarize, all the hard work developed in the study became easier due to great team work.

3.2.5. CLEOPATRE II – *"HPV Type Distribution In Cervical Cancer and in High-Grade Cervical Dysplasia In Portugal - A CLEOPATRE II Study"*

Rational

As consequence of the good results obtained in the CLEOPATRE study and it is underlying in the previous study the information on HPV is scarce in Portugal, more specifically concerning type distribution in CIN2/3 and invasive cervical cancer.

This study was thought and developed by the intervenient of the CLEOPATRE Portugal study group.

Objectives

This study had the main objective of estimate the HPV type-specific prevalence in histological samples with high-grade cervical dysplasia and invasive cervical carcinoma diagnosis registered between January 2008 and May 2009, and was conducted in 7 CLEOPATRE Study Sites. 646 histological samples were evaluated.

Responsibilities

As I was responsible for this study implementation, the tasks developed as CPM in study were more enlarged comparing with CLEOPATRE.

Initially, I was responsible to adapt, write and prepare the essential documentation, as the protocol, informed consent and specific logs.

I have conducted all the authority submissions (CNPD and each Administration Board/local Hospital Ethics Committee). I also prepared the Hospital' contracts and was responsible for the negotiation in some specific sites.

After obtain the approvals, the SIVs were prepared and conducted together with the CRA. I also prepare the template of Investigator Site File.

Similarly to Cleopatre study, I was also responsible for National investigator's meetings preparation together with Sponsor and CLEOPATRE Portugal Study Group. Weekly evaluation on study status was made together with sponsor, where the planned national recruitment and corrective actions implementation to improve it were frequently discussed.

In what concerns to internal matters, at KeyPoint CRO, the trial costs were evaluate in a monthly frequency, team management, monitoring plan preparation and evaluation of timelines.

This study had a logistic samples (shipment of cervical excision specimen's blocks from the sites to a central lab) that I was responsible for define it – the shipment frequency, person of contact in each site, day or time of collection and samples preparation.

Main Results

HPV 16 is the most common HPV type across the high-grade cervical lesions and invasive cervical cancer, as observed worldwide. These data provide a better knowledge of the HPV type distribution in Portugal and across Europe[15] .

Personal Perspectives

This study had the particularity to include clinical data from death women, with the main purpose to not bias the results by including only alive women. Consequently, this study gave me training on how to argue such matters with the authorities.

This study had huge logistic issues, as biopsies shipment to a central anatomopathology lab for histopathological review. The responsibility of order all the material and shipments in a timely manner taught me to manager a large number of issues and difficulties felt by different people.

I would like to emphasize that even I have prepared some Investigators Meeting in Cleopatre, in this second study these meetings preparation gave me an additional pleasure as it was as if we were driving a research path about this disease and that seemed to have no end. We were already in the second study and in each investigator meetings all the highly motivated physicians were always waiting for listen the results obtained from a large teamwork.

3.2.6. PRIMS – "*Surveillance Study to Estimate the Incidence of Pure Red Blood Cell Aplasia Among Patients With Chronic Kidney Failure (PRIMS)*"

Responsibilities

In the beginning of 2009, I was designated as Project Manager of this study. I was also involved in the final recruitment, motivating the CRA team in order to achieve the patients target.

This study was already detailed above in CRA Studies. Concerning the CPM tasks, I would like to highlight the weekly updates sent to the Sponsor in other to keep a close communication. It was also carried out weekly teleconferences with the Sponsor in order to evaluate specific issues to solve site by site.

It was also performed a close evaluation of pending queries. With this strategy and good communication with the sites all the queries were solved in a timely manner.

Due to study extension, near the end of study it was needed the trial costs evaluation, prepare amendment to Sponsor proposal/financial agreement and timelines evaluation.

I was also responsible for the management of the study close-out and for notifying the investigators and Hospital Administration Board about this.

Rational and Objective described at point 3.1.7.

Personal Perspectives

I appreciated work with this Sponsor, it was a great experience. Some difficulties/obstacles in study progress were identified and proactive actions were carried out with Sponsor agreement whose facilitate successful outcome of the study in Portugal.

3.2.7. ÉVORA – "*Estudo de aValiação de Opções terapêuticas de 3ª linha de QT em doentes com CPNPC que fizeRam inibidores TK em 2ª linhA – ÉVORA; Study to evaluate the third-line treatments non-small cell lung cancer in patients who performed tyrosine kinase inhibitor in second-line.*"

Rational

The definition of the best strategy for action in relation to the available drugs for the treatment of NSCLC considering the several therapeutic options in multiple lines is one of the questions that can be raised. The choice of treatment options of the first lines determines the choices on subsequent lines. In this context, it is important to analyze what the profile of choice after use (and failure) of options established as effective in the 1st and 2nd rows

Objectives

Characterization of therapeutic options in 3rd line chemotherapy in patients with NSCLC treated with TK inhibitors in 2nd line.

Responsibilities

In this study I was responsible for the contact with Sponsor. The study involved a national Sponsor composed by a group of physicians.

I was also responsible to discussed with the National Coordinator the final version of CRF designed by the Data Management Department of KeyPoint CRO. This study involved an electronic CRF.

In addition to the above mentioned tasks I also ensure the study initiation, which includes responsibilities as guarantee that all regulatory submissions were done and respective approvals were obtained and that all relevant documentation was obtained from study sites.

During this period, I finished the collaboration with the KeyPoint CRO, so all the issues concerning the study development was carried out by other KeyPoint CRO team member.

Main Results

The final results are being evaluated. The statistical report is on elaboration.

Personal Perspectives

Évora study was my second study in Oncology, but was the first study which forced me to have specific training due to different types of lung cancer and specificity of this disease.

With this study I had my first contact with this group. The GECP emerged 11 years ago as a result of the need to join efforts in promoting awareness of Pulmonary Oncology with main goals of

boosting the development of oncology units with an interest in lung cancer; facilitate and encourage the sharing of experiences and foster research creating structures to support clinical research.

3.2.8. CREDIT – *"Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy - Long-Term International Non Interventional Study In People With Type 2 Diabetes, Treated With Insulin".*

Rational

The aim of the CREDIT study was double: to establish in real life the relationship between blood glucose control and cardio-vascular events and to collect data that will reflect current practices in the management of patients with type 2 diabetes mellitus.

This multinational non-interventional study focused on type 2 diabetic patients on insulin seen by specialists in diabetes and general practitioners who are experienced in insulin therapy (initiation and titration). It will provide a multinational perspective to identify practice differences across countries, and evaluate compliance to international guidelines of management of diabetes in different areas of the world. The standardization of the data collection process and the data analysis will justify international comparisons.

This very large database will provide supportive data for international recommendations in terms of insulin therapy, in order to more globally improve quality of medicine usage. It will also support future exploratory researches on the cardio vascular platform with people with type 2 diabetes mellitus.

Objectives

The main objectives are the observation of medical practice in the real life, over a 4-year period, in people with type 2 diabetes treated with insulin, and the evolution of the glycaemic control and its relationship with Cardiovascular (CV) events.

Responsibilities

This study was passed to KeyPoint CRO after the end of recruitment, where some of the sites involved were already closed.

My responsibilities were related with study conduction, as prepare the monitoring plan, prepare and perform co-monitoring visits and evaluate the CRAs performance.

When the study was allocated to KeyPoint CRO, all the study documentation and essential documents was review (namely sites administration approvals and Financial Agreements).

The study costs were assessed and every 6 months it was evaluated with the sponsor the performed tasks and correspondent amount to be paid.

A weekly updated was sent to Sponsor and when necessary teleconferences or personal meeting were carried out.

Main Results

Study Ongoing

Personal Perspectives

During the study conduction, CRAs team undergone several changes which difficult the contact with the sites.

This brought some constrains with the Sponsor which put me in test as study manager. However, this was overcome as the study management was made always by the same person the Sponsor felt this issue less significant.

3.2.9. INSPIRE-ME-IAA – *"INternational Study of Prediction of intra-abdominal adiposity and its RElationships with CardioMEtabolic Risk /Intra-Abdominal Adiposity"*

Rational

INSPIRE ME IAA will provide direct assessment of IAA (CT scan) as well as capture prospectively the incident cardiometabolic events during a follow-up period of 3 years. As a worldwide study that is designed to be methodologically rigorous with a central reading for the CT scans and a central laboratory for all the metabolic tests, this study will provide scientific evidence of the link between intra-abdominal adiposity and occurrence of cardiovascular and metabolic diseases and will allow to compare the strength of this relationship in different parts of the world.

Objectives

Determine the relationship between intra-abdominal adiposity and

- cardiometabolic risk markers/factors including waist circumference;
- history of ischemic cardiovascular events and type 2 diabetes.

Prospectively, determine the relationship between intra-abdominal adiposity and incidence of type 2 diabetes and ischemic cardiovascular events over a 3-year follow-up period.

Responsibilities

Similarly to CREDIT study, this project was allocated to KeyPoint CRO after the end of recruitment.

My responsibilities were also related with study conduction and study documentation revision, in order to evaluate possible pending documents that could be collected during the study conduction (namely study team updated CVs).

The management also involved the assessment of the study costs. Where at every 6 months it was evaluated with the sponsor the performed tasks and the amount to be invoiced accordingly.

A weekly updated was sent to Sponsor and when necessary teleconferences or personal meeting were carried out.

Main Results

Study Ongoing

Personal Perspectives

As mentioned in CREDIT study, in this project the CRAs team also undergone several changes that forced to strategies creation to maintain the sites motivated to continue the protocol procedures and keep them informed about the main contact in case of any difficulty.

Due to the good relation with the Sponsor strategies were created and both studies were carried out successfully and with study teams very motivated.

4. Description of the work developed at Boehringer-Ingelheim - Portugal

Boehringer Ingelheim's successes in research & development continuously strengthen their portfolio of medications. The company focuses on six major research areas: CardioMetabolic diseases, Central nervous system diseases, Immunology and Inflammation, Infectious diseases, Oncology and Respiratory diseases.

In Portugal, this company continues with local CRAs, without CRO outsourcing to perform the clinical trials monitoring.

4.1. Clinical Research Associate

The tasks developed by me in this company as CRA are mainly related with Clinical Trials conduction and studies monitoring (namely ensure that all studies are being compliant with GCP and national laws, assure the correct and updated archiving of clinical trial' documentation at the site, guarantee the data quality, verify all issues related with Investigational Medicine Product, perform On Site Monitoring Visits and assure the site pharmacovigilance compliance).

As all the clinical trials are ongoing there is no mention to the topic main results per study.

In the table below, it is not present the Recruitment Period for clinical trials Tomorrow Roll-Over Study neither BI1199.33 as these trials are a roll-over studies and the recruitment is not related with the recruitment time but with the number of patients included in the clinical trial Tomorrow and Inpulsis-2, respectively.

Table 3 - Number of sites, number of included patients, recruitment period and therapeutic area per study, as CRA at Boehringer-Ingelheim

Study	Sites #	Patients Enrolled #	Patients Randomized #	Recruitment Period (months)
Tiospir	8	106	104	7
TOnado-1	7	74	63	10
Inpulsis-2	5	28	20	12
Tomorrow Roll-Over	4	6	6	-
BI1199.33	5	Ongoing	-	-

4.1.1. TIOSPIR – *"Randomized, Active-controlled, Double-blind, Double-dummy, Parallel Group Design, Multi-center Trial to Compare the Efficacy and Safety of 2.5 µg and 5 µg Tiotropium Inhalation Solution Delivered by the Respimat Inhaler With Tiotropium Inhalation Capsules 18 µg Delivered by the HandiHaler"*

Rational

According to the Global Initiative on Chronic Obstructive Lung Disease (GOLD) guidelines[1617], chronic obstructive pulmonary disease (COPD) is "*…a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases*."

There is no cure for COPD and, other than smoking cessation, there are no interventions that have been definitely shown to slow the accelerated of loss of lung function that is characteristic of COPD. Nevertheless, present treatment options are effective for the relief of symptoms, improving exercise tolerance and health-related quality of life as well as preventing COPD exacerbations.

Both formulations of tiotropium have been developed for the maintenance treatment of COPD. Tiotropium HandiHaler® 18 µg once daily is approved for use in over 100 countries worldwide with market introduction in Europe in 2002 and subsequently in other countries including the United States (approval in 2004). Tiotropium Respimat® 5 µg once daily was developed as an alternative to the HandiHaler® formulation and is currently approved in more than 60 countries with initial approval in 2007. The dose of 5 µg was determined to provide comparable pharmacokinetic and pharmacodynamic properties to the HandiHaler® formulation at 18 µg once daily.

Direct comparison studies of the tiotropium HandiHaler® 18 µg and Respimat® 5 µg formulations have been limited to 4-week crossover studies.

This clinical trial is registered in the ClinicalTrials.gov (NCT01126437).

Objectives

Prospective data acquisition from a trial of adequate size and duration was planned to establish that compared to tiotropium HandiHaler®, tiotropium Respimat® will have (a) similar effects on safety and (b) similar or superior effects on exacerbations.

The primary outcomes are the time to first COPD exacerbation and time to death.

Responsibilities

As I was allocated to this study after the end of recruitment, my responsibilities are related with Clinical Trial conduction and study monitoring, previously detailed.

Personal Perspective

With this clinical trial with so many patients randomized, there are several different issues to solve every day. The sites study team requests our support frequently in order to avoid Protocol Violations.

The most acknowledgment acquired with this study is related with the pathology and the study medication.

This was my first clinical trial with so much patients and compliances to verify in the pharmacy's sites which force me to plan longer monitoring visits.

4.1.2. Tonado-1 – *"A Randomised, Double-blind, Parallel Group Study to Assess the Efficacy and Safety of 52 Weeks of Once Daily Treatment of Orally Inhaled Tiotropium + Olodaterol Fixed Dose Combination (2.5 µg / 5 µg; 5 µg / 5 µg) (Delivered by the Respimat® Inhaler) Compared With the Individual Components (2.5 µg and 5 µg Tiotropium, 5 µg Olodaterol) (Delivered by the Respimat® Inhaler) in Patients With Chronic Obstructive Pulmonary Disease (COPD). [TOnado TM 1]"*

Rational

As mentioned above, Tiotropium Respimat® 5 µg once daily is currently approved in more than 60 countries with initial approval in 2007.

ERS, ATS and GOLD treatment guidelines all place bronchodilators as the foundation of pharmacologic management of COPD. In patients with moderate to very severe pulmonary impairment whose symptoms are not adequately controlled with as-needed short-acting inhaled bronchodilators is recommended.

Objectives

In this clinical trial, the primary objective of this study is to assess the efficacy and safety of 52 weeks once daily treatment with orally inhaled tiotropium (LAMA) + olodaterol (LABA) FDC (delivered by the RESPIMAT Inhaler) compared with the individual components (tiotropium, olodaterol) (delivered by the RESPIMAT Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD).

This clinical trial is registered in the ClinicalTrials.gov (NCT01431274).

Responsibilities

I was allocated to this study in the before study implementation. So, I have prepared all national and international documentation for submission to Competent Authorities, Ethics Committee, CNPD and to Administration Board of each site.

I was also involved in Investigator Site File and Pharmacy File preparation.

As CRA I was also requested to ensure that all the study supplies were in the site before each initiation. The Site Initiation Visits were all carried out in a timely manner after obtain the approvals.

Now, as the recruitment ended my responsibilities are related with the trial conduction and monitoring.

Personal Perspective

The recruitment plan for Portugal was 60 patients. At the end of recruitment it was achieved a 105% of the planned.

This involved a great work team between the both CRAs allocated to this study and required a good acknowledgment of the clinical trial protocol as the sites raised frequently questions related to protocol procedures and eligibility criteria.

4.1.3. Tomorrow Roll-Over Study – *"A Phase II Open Label, Roll Over Study of the Long Term Tolerability, Safety and Efficacy of Oral BIBF 1120 in Patients With Idiopathic Pulmonary Fibrosis"*

Rational

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown aetiology that is characterized by progressive fibrotic destruction of the lung, resulting in disabling dyspnea and poor gas exchange. The average life expectancy in IPF patients is 2-3 years. No preventive approach or globally accepted treatment other than lung transplantation and enrolment in clinical trials is currently available. Only recently pirfenidone has been approved in Japan and India. There is an unmet medical need for treatments in IPF.

BIBF 1120 has been studied in a large Phase 2 trial (1199.30) in patients with IPF and in this first study the drug has shown promising effects in reducing the rate of decline of forced vital capacity and reducing exacerbation, as well as several other endpoints[18].

This clinical trial is registered in the ClinicalTrials.gov (NCT01170065).

Objectives

The aim of this trial is to offer continuation of BIBF 1120 treatment for patients with Idiopathic Pulmonary Fibrosis (IPF) who have completed a prior clinical trial with that drug.

The primary objective will be to establish the long term tolerability and safety profile of BIBF 1120 in IPF.

As a secondary objective the effects of long term treatment with BIBF 1120 on survival as well as safety and efficacy parameters will be investigated in an open-label, not randomized, un-controlled design.

The primary outcome is the Forced vital capacity decline.

Main Responsibilities

My responsibilities are related with Clinical Trials conduct and study monitoring.

Personal Perspective

As this is phase 2 roll-over study, there already exists a close relationship between the monitors and the site teams which makes monitoring easier (as these study teams are well structured and recognize the monitoring function as a gain to improve their work).

I also realized that the older is the relationship with the sites greater is the work recognition turning it more gratifying.

4.1.4. Inpulsis-2 – *"A 52 Weeks, Double Blind, Randomized, Placebo-controlled Trial Evaluating the Effect of Oral BIBF 1120, 150 mg Twice Daily, on Annual Forced Vital Capacity Decline, in Patients With Idiopathic Pulmonary Fibrosis (IPF)"*

Rational

According to the above mentioned about IPF and the large Phase 2 trial (1199.30), the purpose of this trial is to investigate and confirm the efficacy and safety of BIBF 1120 at a high dose in treating patients with IPF, compared with placebo. The trial is being conducted as a prospective, randomised design with the aim to collect safety and efficacy data.

This clinical trial is registered in the ClinicalTrials.gov (NCT01335477).

Objectives

Respiratory function is globally accepted for assessment of treatment effects in IPF patients. The chosen endpoint (Forced Vital Capacity decline) is easy to obtain and is part of the usual examinations done in IPF patients.

Main Responsibilities

When I was allocated to this study, the project was at the same point as Tonado (mentioned above), so my responsibilities were similar.

In this study the recruitment exceeded the panned (120% was attained to this clinical trial).

Personal Perspective

Like mentioned in TOnado study, it was developed a great work team between the both CRAs allocated to this study in order to attain the recruitment already mentioned.

I have learned to stimulate and motivate the site teams in order to improve the recruitments and create achievements with site teams (always above the expected) in order to motivate themselves to achieve it. At the end of the recruitment it was very grateful to see that the high initial recruitment target was areached and exceeded.

4.1.5. BI 1199.33 – *"An Open-label Extension Trial of the Long Term Safety of Oral BIBF 1120 in Patients With Idiopathic Pulmonary Fibrosis (IPF)"*

Rational and Objectives

The aim of this extension trial is to provide BIBF 1120 treatment for all patients who have completed one year treatment and the follow up period in the double-blind phase III placebo controlled parent trials (1199.32 and 1199.34), who may have experienced benefit from the drug and wish to continue treatment with BIBF 1120.

The planned enrolled patients in all participating sites/countries are 750. In Portugal the recruitment has not started yet but there are 20 patients eligible (number of patients randomized in Clinical Trial BI 1199.34).

This clinical trial is registered in the ClinicalTrials.gov (NCT01619085).

Responsibilities

In this study I was responsible to prepare all national and international documentation for submission to Competent Authorities, Ethics Committee, CNPD and to Administration Board of each site.

I was involved in Investigator Site File and Pharmacy File preparation.

Until this time point, there are no patients included in this trial as no patient has finalized the clinical trial BI1199.34.

Personal Perspective

This roll-over studies the sponsor provide treatment to all patients who have completed the clinical trial where had the first contact with trial drug. So, there are no pressure related to recruitment and the trial becomes easier to implement.

5. Discussion

Along this report, it was presented all the studies which I was involved, the main activities I have developed and my personal perspective about each study and experience.

I have noticed that it is essential a thorough understanding of Study Protocol (more specifically the flow chart, planned visits per patient and procedures per visits) and all study supportive documents (Informed Consent Form, CRF). An instrument that has proved as an important tool for management and monitoring guide is the Monitoring Plan.

The acknowledgment in Regulatory issues and study's methodology are also essential for the good study's conduction. This last item became crucial in CPM function.

Beyond knowledge acquired throughout the work performed, there were academic needs emerging.

During the collaboration time at KeyPoint CRO, I have received regular training in clinical trial audit, specific pathologies/diseases and regulatory requirements in Non-Interventional Studies/Clinical Trials.

Whenever necessary, the Sponsor provided information about the investigational product and other training related with a specific clinical study, forms and/or SOPs.

Due to knowledge gaps early discovered in beginning of CRA work, I attended the Post-Graduation course in Clinical Trials Monitoring (at Lusófona University, Lisbon).

After assuming the role as CPM, despite the large experience as monitor I felt the need to complement the knowledge with updated information covering other research areas.

In recent years, the new paradigm of Personalized Medicine "The Right Molecule, at the Right Dose, in the Right Patient" made me though about the training needs on more specific matters as Translational Medicine, Product Research and Development Process, Regulatory Affairs, Safety and Risk Management, Pharmacoeconomics (those are some examples of Curricular Units/themes covered in Master in Pharmaceutical Medicine).

Along the course I had been provided with several perspectives from different lectures, namely CROs and industry employees.

In a personal level these differences were sustained by the experience that I have felt when I move from CRO to industry.

My experience at KeyPoint CRO allowed me to follow the study since Sponsor/Investigator idea followed by Protocol elaboration until the medical writing. I had the opportunity to be part of various projects, in different therapeutic areas and be familiar with different units (eg. data management, statistics).

This work had some disadvantages as the need to be familiar with various SOPs, to report to a large number of clients and manage their own expectations about their studies.

The core business of this CRO is the non-interventional studies. Those studies usually have a huge number of sites and patients with simpler procedures but with a high logistic associated in opposition to the Clinical Trials.

The involvement in this type of studies allowed me to acquire a thought more practical to deal with the several obstacles appeared in the different studies.

By assuming the role of CPM these studies also allowed me to develop aspects of time management, motivation and conflict management among the team.

My experience in the industry is exclusively clinical trials. In those studies it is important to highlight the rigorous procedures with specific timelines which requires from the CRA a stricter site study teams control.

On the other hand, to be part of Sponsor team, we just need to be familiar with their own specific SOPs which turn into less time-consuming in opposite to a CRO when we have to deal with a variety of sponsors.

Regardless of the therapeutic area, type of study, or even the function or the role that you take (sponsor or subcontractor), the focal point for the study success is the good communication between all the parts involved from site, passing through monitor, project manager until sponsor.

6. Conclusion

The experience acquired in the field as CRA and the knowhow obtained as CPM contributed to a better acknowledgment of the perspectives and expectations from the different stakeholders.

With reporting of my experience I would like to demonstrate the main difficulties/barriers felt in different studies and different phases of clinical research, allowing those obstacles evaluation by others (for instance as demonstrated in the situations where private clinics were involved, the recruitment period was longer giving the opportunity to achieve the recruitment target).

Since I have started my professional work, I have contributed to the clinical research development in Portugal. Although my contribution alone is small I consider that being part of those who believes in clinical development as the key to find new innovative products in a shorter period of time.

7. References

[1] Congressional Budget Office. Research and Development in the Pharmaceutical Industry. 2008

[2] European Commission. Innovative Medicines Iniative, Better tools for better medicines. 2008.

[3] US Food and Drug Aministration. Critical Path Opportunities. 2006 March; [cited 2011 February 25]. Available from:

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf

[4] The Innovative Medicines Iniative (IMI) Research Agenda. Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society. 2008 February 15.

[5] Tufts center for the study of drug development, 2007

[6] Note for Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2). Step 4. 2009 June.

[7] ICH E8 Guideline: General Considerations for Clinical Trials; 1998 March.

[8] International Conference on Harmonisation; [cited 2012]. Available from:

http://www.ich.org/about/history.html

[9] França A. et al. Venous Thromboembolism Risk Factors and Practices Of Prophylaxis -Endorse Study Results in Portugal. Acta Med Port 2011; 24: 951-960.

[10] Olivares JM. et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). Eur Psychiatry. 2009 Jun;24(5):287-96.

[11] Nunes, P. et al. "Methodological data and main issues encountered during a portuguese registry on prostate cancer – ReNaCaP"

[12] Nunes, P. et al. National Registry of Prostate Cancer, in Portugal – ReNaCaP. Acta Urologica. 2010 Sep;3: 39–45.

[13] Pista A. et al. CLEOPATRE Portugal Study Group. Prevalence of Human Papillomavirus Infection in Women in Portugal: The CLEOPATRE Portugal Study. Int J Gynecol Cancer. 2011 Aug; 21(6):1150-8.

[14] Costa, A. R. et al. Impact of a women's counseling programme on combined hormonal contraception in Portugal – The IMAGINE Study. The European Journal of Contraception and Reproductive Health Care, 2011; 00: 1–9.

[15] Oliveira C. et al. CLEOPATRE Portugal Study Group. HPV Type Distribution In Cervical Cancer And In High-Grade Cervical Dysplasia In Portugal - A Cleopatre II Study, Portugal. ESGO Milan 2011

[16] Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2008. http://goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003 (2008).

[17] Fromer L., Cooper CB. A review of the GOLD guidelines for the diagnosis and treatment of patients with COPD. Int J Clin Pract 2008;62(8):1219-1236.

[18] Richeldi L. et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011 Sep 22;365(12):1079-87