Universidade de Aveiro Secção Autónoma das Ciências da Saúde
2015

VANESSA SOFIA SILVA VALENTE

Curricular Training Report as a Clinical Research Coordinator in Blueclinical Ltd

Relatório de Estágio Curricular como Coordenadora de Investigação Clínica na Blueclinical Lda

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Relatório apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro e da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical Lda.

"*Personal relationships are the fertile soil from which all advancement, all success, all achievement in real life grows*"

Benjamin Jeremy Stein

o júri

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agradecimentos

Começo por agradecer à minha família, porque representam o princípio de todo este percurso: aos pais, que sempre me apoiaram e continuam a apoiar; e aos irmãos, sem eles a vida não tinha a cor que tem.
Agradeço ao Fábio Martins, por todo o amor e por nunca desistir. Sem ele, não era a mesma coisa.

Às minhas “amiguinhas” Andreia Rocha, por todas as gargalhadas e momentos bem passados e, em especial, à Patrícia Ferreira, a minha companheira de aventuras e desventuras durante este longo percurso universitário. Obrigada pela amizade!

Ao Professor Luís Almeida e Professor Sérgio Simões pela oportunidade, à Doutora Cristina Lopes pela orientação nesta experiência profissional e ao Professor José Carlos Lopes pela orientação na escrita deste relatório.

À Sónia Correia, Rita Espanhol e Daniela Cabeleira, porque me terem ensinado tudo o que sei hoje. À Catarina Gomes pelo companheirismo e amizade.

A toda a equipa da Blueclinical por serem fantásticos, em especial à Ana Correia pela amizade e paciência.

palavras-chave

Blueclinical, coordenadora de investigação clínica, ensaios clínicos, estudos observacionais, investigação clínica, centro de investigação clínica

resumo

O presente relatório descreve as atividades desenvolvidas no âmbito do estágio curricular como coordenadora de investigação clínica na área de negócio "*Clinical Research Partnership*" da Blueclinical. O estágio curricular teve a duração de 10 meses – Julho de 2014 a Abril de 2015.

Este relatório fornece uma visão geral da implementação de ensaios clínicos e estudos observacionais em centros de investigação clínica em paralelo com a minha experiência durante os 10 meses de estágio curricular como coordenadora de investigação clínica no Centro Hospitalar de Vila Nova de Gaia/Espinho. Para permitir a compreensão das normas segundo as quais a minha atividade foi desenvolvida, é feita uma contextualização da investigação clínica no que respeita ao enquadramento legal, ético e evolução do número de ensaios em Portugal ao longo dos últimos anos.

No cômputo geral, experimentei uma grande melhoria na compreensão da coordenação de ensaios clínicos e estudos observacionais, assim como a nível de "*soft skills*".

keywords

Blueclinical, clinical research coordinator, clinical trials, observational studies, clinical investigation, clinical research center

abstract

This report describes the activities developed within the curricular internship as a clinical research coordinator in the Clinical Research Partnership business area of Blueclinical. The internship lasted 10 months – from July 2014 until April 2015.

This report provides a general view of the implementation of clinical trials and observational studies in clinical research centers alongside with my experience during the 10 months of curricular internship as a clinical research coordinator in *Centro Hospitalar de Vila Nova de Gaia/Espinho*. To understand the regulations under which my activities were developed, clinical research is contextualized in what regards it's legal and ethical framework and the evolution of the number of clinical trials in Portugal along the last years.

In the overall result, I have experienced a great improvement in understanding the coordination of clinical trials and observational studies, as well as the improvement of my soft skills.

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List of Abbreviations

AB – Administration Board

AE – Adverse Event

ARS – *Administração Regional de Saúde* (Regional Health Administration)

CA – Competent Authority

CDA – Confidential Disclosure Agreement

CEIC – *Comissão de Ética para a Investigação Clínica* (Ethics Committee for Clinical Research)

CES – *Comissão de Ética para a Saúde* (Ethics Committee for Health)

CHVNG/E – *Centro Hospitalar de Vila Nova de Gaia/Espinho* (Hospital Centre of Vila Nova de Gaia/Espinho)

CNPD – *Comissão Nacional para a Proteção de Dados* (National Commission for Data Protection)

COD – Clinical Operations Director

CRA – Clinical Research Associate

CRC – Clinical Research Coordinator

CRF – Case Report Form

CRO – Contract Research Organization

CRP – Clinical Research Partnership

CV – *Curriculum Vitae*

EC – European Commission

EEA – European Economic Area

EMR – Electronic Medical Records

EU – European Union

ECG – Electrocardiogram

EudraCT – European Data Base

FIH – First-in-Human

GCP – Good Clinical Practices

GIC – *Gabinete de Investigação Clínica* (Clinical Research Office)

IB – Investigator Brochure

ICF – Informed Consent Form

ICH – International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IM – Investigator Meeting

IMP – Investigation Medicinal Product

INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (National Drug Authority and Health Products)

ISF – Investigator Site File

IWRS – Interactive Web Response System

MA – Marketing Authorization

MMR – Measles-Mumps-Rubella

MS – Member States

PDD – Pervasive Developmental Disorders

PI – Principal Investigator

PoC – Proof-of-Concept

RA – Regulatory Authorities

R&D – Research and Development

SAE – Serious Adverse Event

SOP – Standard Operating Procedure

WMA – World Medical Association

1. Introduction

My objective with this report is to describe the natural course of clinical investigation and make the parallelism with my curricular internship in Blueclinical – *Investigação e Desenvolvimento em Saúde, Lda* (Investigation and development in Health). As I will specify further on, Blueclinical is composed by three business areas: Blueclinical Phase I, Clinical Research Partnership (CRP) and Research and Development (R&D).

On the 21st January 2014, I started my para-curricular internship for Blueclinical CRP. It took place at *Centro Hospitalar de Vila Nova de Gaia/Espinho* (Hospital Centre of Vila Nova de Gaia/Espinho) – CHVNG/E, one of the partner hospitals of this business area, where I held Clinical Research Coordinator (CRC) functions. On the 1st of July 2014, I started the curricular internship, which will be my focus throughout this report.

I chose to start with the general framework of clinical investigation at the present and then provide details on my particular experience with the curricular internship.

First, I will present the learning outcomes I have defined, the host-institution and the partner hospital where I took my internship during 10 months. In chapter number 2, I will talk about the state of clinical investigation. It is essential to know these topics in order to contextualize my activity. The learning outcomes are firstly mentioned because I had to think of it before starting the internship, in order to stablish goals for my work and, also, because it is one of the starting points for the preparation of this report. I will also describe the activities performed at Blueclinical, the host-institution, and CHVNG/E, because it was at this partner hospital that I have held most of my activities. The state of the art will contextualize my working activity at Blueclinical and I will give special attention to the parts of the activity that I had the opportunity to interact with.

After this, in chapter number 3, I will describe in detail every activity performed during my internship, from the activities related with the clinical trials/observational studies in the hospital, to back-office related activities for Blueclinical headquarters.

It is in the discussion, chapter number 4, where I will confront what I have learnt with the objectives I proposed myself to reach in the beginning. This chapter is very important, because it is where I expose a more personal opinion about what I have learnt, which were my difficulties and what I did to overcome them.

Finally, in chapter number 5, I will state the learning outcomes that I have achieved and the ones I still have to learn on my job career, as a conclusion.

1.1 Curricular Internship Learning Outcomes

The learning outcomes to accomplish throughout my curricular internship activity reflect not only what I should know about the CRC professional activities, but also personal learning outcomes that I would like to improve at the end of this experience.
The knowledge I acquired at university gave me a strong basis to understand the type of activities I was going to perform, however, without the opportunity Blueclinical gave me with the para-curricular and curricular internships I could never acquire the knowledge I now have. Before I started the curricular internship, I already knew what kind of activities I was going to perform, because I did a para-curricular internship as a study coordinator from 21st January 2014 until the 1st of July. Therefore, I established the learning outcomes soon in this process in order to organize myself to achieve them as well as possible. For the definition of these learning outcomes, the para-curricular internship was a very important help, because I already knew which activities I needed to engage myself in, in order to be a complete CRC.
The professional learning outcomes I defined are the following:

- Know how to submit clinical trials and observational studies to a clinical research center;
- Comprehend how to coordinate clinical trials and observational studies from feasibility phase, during its' development, to its' close-out in a clinical research center;
- Comprehend the application of Good Clinical Practices (GCP) during the development of clinical investigation in clinical research centers;
- Comprehend the dynamic of audits and inspections and know how to monitor these processes in a clinical research center.

These learning outcomes cover all the activities I performed during the internship. I also established some personal learning outcomes:

- Develop a good relationship with all investigation teams, patients, Clinical Research Associates (CRA) and Blueclinical co-workers;
- Be able to provide patients with the best experience during their participation in clinical trials;
- Develop soft skills, namely: good communication skills, both oral and written, self-confidence, critical analysis of all situations, organizational skills and conflict resolution.

Once this is defined, it's time to contextualize the reader into the job role I have performed.

In the next section, I will present the host institution and the partner hospital where I developed my internship.

1.2 Host-Institution and Partner Hospital overview

*Blueclinical – Investigação e Desenvolvimento em Saúde, Lda (*Investigation and Development in Health*)*

Blueclinical is the institution that hosted me for my curricular internship from July 2014 to April 2015. Founded in 2012, its' headquarters are located at *Avenida Villagarcia de Arosa, Matosinhos*, city of Porto and it is composed by three business units: Research & Development (R&D), Phase I and Clinical Research Partnership (CRP). These areas are organized in order to provide support to the investigational activity along the phases of clinical investigation, commonly designated as "*from bench to bedside*".

Blueclinical R&D

Blueclinical R&D provides help in the development of new opportunities, such as therapeutic and diagnostic solutions, generated by institutions and companies with the intent of bringing these products to the market. The final objective of this business area is to facilitate translational medicine ("*from bench to bedside*") and clinical investigation for small institutions and companies, such as start-ups. This comprehends the beginning of the investigation process, when R&D projects are translated into investigation in humans.

Blueclinical R&D consultancy is specialized in supporting the design and implementation of pharmaceutical, pre-clinical and clinical regulatory development plans, not only for medicines, but also for medical devices and other health products; planning pharmaceutical development and the respective analytical methods; preparing investigator's brochures (IB) and investigational medicine product (IMP) dossiers; preparing and monitoring scientific and regulatory counselling; and also, very important, Blueclinical R&D supports in the preparation of business plans and financial appliances (1).

Blueclinical Phase I

Blueclinical Phase I facilities are located at Hospital da Prelada, 3rd floor, west wing and were inaugurated on the 12th July 2013. Phase I is a unit of modern facilities, safety and comfort conditions, with 29 beds and experienced staff in clinical trials' phase I conduction. Blueclinical Phase I mission is to conduct first in human clinical trials, which are conducted in healthy volunteers, or proof-of-concept trials in selected patient populations. This business area has an e-mail through which volunteers can apply to participate in these trials. Clinical trials in healthy volunteers have different objectives and, based on the analysis that it is supposed to do, the following types of phase I clinical trials can be performed:

a) bioavailability and bioequivalence trials, to determine the similarity of different formulations of the same medicine (2);
b) food interaction trials, that help determine if medicines must be taken along with food or out of meals (2);
c) drug interaction trials, to determine if the drug's concentration if affected by the intake of other drugs (2);
d) tolerability and pharmacokinetics trials, to determine which are the safe drug's concentrations and the way it is metabolized and eliminated by the body (2).

As healthy volunteers' clinical trials must also obey to ethical and legal laws, before the conduct of the clinical trial, the protocol and other documents must be submitted to the competent authority (CA), Ethics Committee and National Committee of Data Protection (CNPD – *Comissão Nacional de Proteção de Dados*). This component of the process is also supported by this business unit.

Regarding the fact that Blueclinical provides support to the investigational activity along the phases of clinical investigation, Blueclinical Phase I comprehends the second phase of the investigation. Phase I clinical trials represent the first contact between humans and the investigational drug.

Blueclinical CRP

Blueclinical Clinical Research Partnership intends to support investigation at research centers. The basis of this business area lays at the partnership developed with Portuguese research centers and the main objective of Blueclinical CRP is to stablish partnerships with target hospitals in order to develop a network of clinical research sites of excellence (3). These partnerships comprehend hospitals and primary care units that cover all therapeutic areas. The choice of these research centers is based on the large pool of patients that are covered by them. This will facilitate patient recruitment and referral, mostly from primary care units to hospitals (3).

Blueclinical CRP allocate to each hospital a team of highly trained and committed professionals to coordinate clinical trials' and observational studies' activities in order to produce investigation of high efficiency and quality, enhancing centers reputation in order to attract more clinical investigation to our country.

At the moment, Blueclinical CRP has partnership contracts with *Administração Regional de Saúde* (ARS) *Norte* (Northern Regional Health Administration), which comprehends the primary care units, and 10 hospitals, namely:

- *Centro Hospitalar de Trás-os-Montes e Alto Douro, E.P.E.* (Hospital center of Trás-os-Montes e Alto Douro)
- *Centro Hospitalar do Alto Ave, E.P.E.* (Hospital center of Alto Ave)
- *Centro Hospitalar do Baixo Vouga, E.P.E.* (Hospital center of Baixo Vouga)
- *Centro Hospitalar da Cova da Beira, E.P.E.* (Hospital center of Cova da Beira)
- *Centro Hospitalar de Leiria, E.P.E.* (Hospital center of Leiria)
- *Hospital Distrital da Figueira da Foz, E.P.E* (District Hospital of Figueira da Foz)
- *Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E.* (Hospital center of Vila Nova de Gaia/Espinho)
- *Hospital Garcia da Orta, E.P.E.* (Hospital Garcia da Orta)

- *Unidade Local de Saúde do Alto Minho, E.P.E.* (Local healthcare unit of Alto Minho)
- *Unidade Local de Saúde Matosinhos, E.P.E.* (Local healthcare unit of Matosinhos)

Each hospital has a Clinical Research Office, that have different designations for different hospitals, which is coordinated by a physician from the hospital's board, a supporting office composed by CRCs and every physician that collaborate with the Clinical Research Office as investigators. The coordinator is named by the Administration Board (AB) of each hospital, and its main function is to integrate the office within the institution.

Centro Hospitalar de Vila Nova de Gaia/Espinho

Although the host-institution of my internship is Blueclinical, I performed most of my activities in CHVNG/E, reason why I believe it is important to include this partner hospital in this chapter.

CHVNG/E is a public corporation divided in 3 units: I – previously known as *Hospital Eduardo Santos Silva*, II – previously known as *Hospital Distrital de Vila Nova de Gaia*, and III – previously known as *Hospital Nossa Senhora da Ajuda*. It represents one of the main assisting hospitals of the north of the country, because it covers all the range of healthcare services, from ambulatory and admission multipurpose care, medical and surgery care, to polyvalent emergency department, long-term care and rehabilitation for paediatric, adult and elderly population (4). It possesses every basic, intermediate, differentiated and almost all highly differentiated types of care. This makes CHVNG/E a hospital with a great assistant profile and with a wide range of care services diversity.

CHVNG/E influence area comprehends 700.000 inhabitants (5). It includes: Vila Nova de Gaia, Espinho and Entre Douro e Vouga councils and also councils from the north of the country, above Vouga River.

CHVNG/E, Unit I, has most of the specialties services, including the emergency room for all age groups and polyvalent concerning the types of care available. Also, most beds and technical means are located at Unit I. This allows this hospital to be a research center with high potential, because it can receive many types of clinical trials and observational studies, from the most complex, that require hospital admission of patients and day hospital treatments, to the most simple of all.

The clinical research office is located at CHVNG/E Unit I and is designated *Gabinete de Investigação Clínica* (Clinical Research Office) – GIC. In the hospital, the clinical research office is incorporated into the support of the provision of care area, human resources unit, training, education and research service.

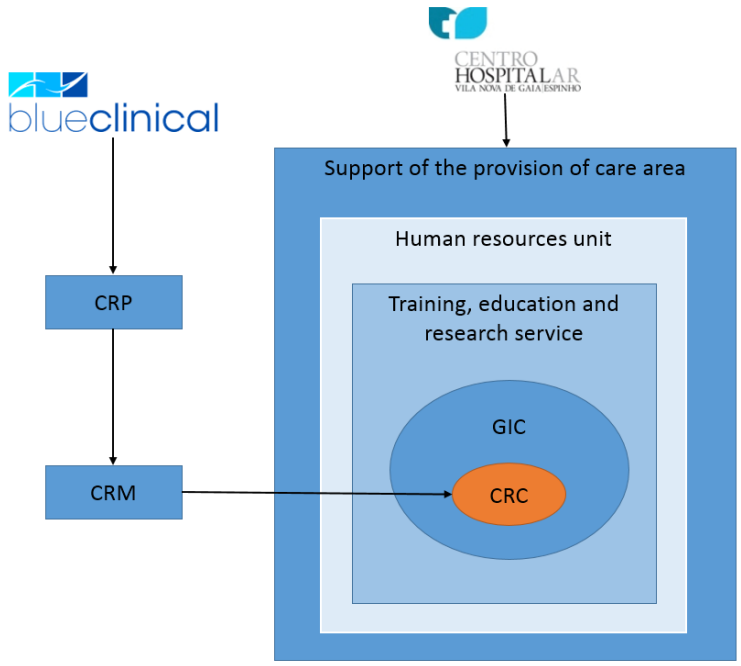

Figure 1 – CRCs within Blueclinical's and CHVNG/E's organization.

Within the CRP business area of Blueclinical are CRCs and each hospital has a Clinical Research Manager (CRM) responsible for it. Within CHVNG/E, CRCs are part of the support office of GIC. (6,7)

2. Clinical Research State of the Art

Clinical investigation is a very complex area, because of the many concepts inherent to this activity. Since it is not possible to mention every aspect, I made a selection of the topics I considered the most important in order to contextualize the reader into my internship.
In this chapter, I intend to explain what clinical trials and observational studies consist in, their legal context, the state of clinical research in Portugal and, finally, the course of studies since its initiation until its approval and termination on a clinical research center. I will start with contextualization of clinical research activity and, second, I explain the implementation of clinical research in a clinical research center. First, it is important to know what clinical trials and observational studies are and how they are classified, to understand the basis. Then, their legal and ethical context, because it was within these rules and guidelines that I held my activity, and I will contextualize the reader about the state of clinical trials in Portugal, in order to know how many clinical trials have been in course. Finally, the process that leads to the implementation of a clinical trial or an observational study in a clinical research center, because this is actually the part of the whole process that I was involved in during the internship. Along this last subtopic, I will mention the main stakeholders involved in this process.

2.1 Context of clinical research

Pre-clinical Phase

Prior to clinical trials in humans, drugs are first studied in animals, designated as non-clinical studies. In this phase of the process, *in vivo* and *in vitro* studies allow investigators to get to know the pharmacological profile of the new drug and develop a rationale for its potential efficacy (8). When conclusions about preliminary tests are drawn, it is time to decide if that drug will move from the “discovery phase” to the “development phase”, where it will start to be tested in humans. At this point, it is very important to make good, reliable predictions about the responses of humans to the drug from the studies in animals (8).

There are 2 primary types of studies that allow testing new drugs or procedures and/or compare between 2 competing drugs or procedures: clinical trials and observational studies (9).

Clinical Trials

Drug development is a process that requires a logical rationale in order to preview which types of studies must be performed earlier to provide information to support and plan larger and more definitive clinical trials (10). The development of drugs is a process often described as consisting of 4 temporal phases:

- Phase I clinical trials are performed in order to define the tolerability, pharmacokinetics and pharmacodynamics in humans, in this phase the objective is not to evaluate the treatment capability of the drug (11). Usually healthy male volunteers are included in these clinical trials, and a small number of volunteers are part of them (dozens). If the drug have significant potential toxicity, then it is studied in patients that have the target disease (10) and not in healthy volunteers.
- Phase II clinical trials are performed in dozens to few hundreds of patients with the target disease to determine preliminary safety and efficacy profile (11). This is where investigators start evaluating which doses will be used for larger clinical trials.

Both phases I and II clinical trials are included in the exploratory development of drugs, where the objective is to reject the bad drug candidates as early as possible in order to save resources to invest in good drug candidates. Every new step is a new opportunity to critically analyze the drug and decide if it demonstrates to be a good candidate to continue investing on it (go/no-go decisions).

The judgement of whether to move from exploratory development to full development phase or not, is a very important decision point. There must be a lot of knowledge about the drug in study, because the full development phase of an investigation process requires a big amount of resources invested and this is not justified if there is no full confidence in the product.

- Phase III clinical trials are wide-scale pivotal studies performed to confirm safety and efficacy of the drug in study (11). In these trials, hundreds to thousands of patients from all over the world are included.
- Phase IV clinical trials are performed after the drug is commercialized, they intend to prove safety or compare the study drug with other therapies (11). The patient population included in these trials is not as strict as for clinical trials from phases I, II or III, because the intention is to approach the study population to the normal clinic.

Figure 2 resumes very briefly what has been explained above.

Figure 2 – Phases of clinical development from pre-clinical to post-market studies.
For each phase of development it is presented the types of studies performed. (Adapted from (12).)

As shown in Table 1, the different phases of clinical trials may also be designated according to the study objectives they hold:

- Phase I: human pharmacology. These studies represent the first in humans and are performed in healthy volunteers so, the purpose is to know the effect that the drug has on the body, what the body does to the drug and also, to comprehend the interactions between drugs and the relation between the study drug and food ingestion. The purpose of these trials does not have to do with the desired effect of the drug on the disease.
- Phase II: therapeutic exploratory. This phase of clinical trials is when the effect of the drug on the disease is explored for the first time. For these studies, patients with

the target disease are included and the inclusion criteria are demanding and narrow (10).

- Phase III: therapeutic confirmatory. Phase II clinical trials intend to explore the therapeutic value of the drug and phase III clinical trials intend to confirm conclusions from previous trials and to make more definitive conclusions. They not only confirm efficacy, but also continue studying safety and quality of the drug.
- Phase IV: therapeutic use. Finally, phase IV clinical trials are performed after drug commercialization, because they are not needed for drug approval, but are important to optimize the drug's use (10).

Table 1 – Phase, respective type of trials, its' purpose and examples of clinical trials.
(Adapted from table 6.1 of (11).)

Phase	Type of trial	Purpose of trial
I	Human Pharmacology	Assess tolerability Define Pharmacokinetic and Pharmacodynamics Explore drug metabolism and drug interactions Estimate activity
II	Therapeutic Exploratory	Explore use for the targeted indication Estimate dosage for subsequent trials Provide basis for confirmatory trial design, endpoints and methods
III	Therapeutic Confirmatory	Demonstrate/confirm efficacy Establish safety profile Provide an adequate basis for assessing the benefit: risk relationship to support licensing Establish dose response relationship
IV	Therapeutic Use	Refine understanding of benefit-risk relationship in general or special populations and/or environments Identify less common adverse reactions Refine dosing recommendations

According to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline E8, "*It is important to recognise that the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases (…). A classification system using study objectives (…) is preferable*" (10). As shown in Figure 3, one type of study may occur along the different phases of development of a drug (10), this justifies why the phases of development are not the best way to classify clinical trials. For example, human pharmacology studies are usually conducted during Phase I, however, such studies are also conducted during other phases of development, despite they are still considered Phase I clinical trials due to the characteristics of the studies. Throughout the development, during large clinical trials, it may become necessary to perform additional studies from earlier phases in order to clarify some issues (10).

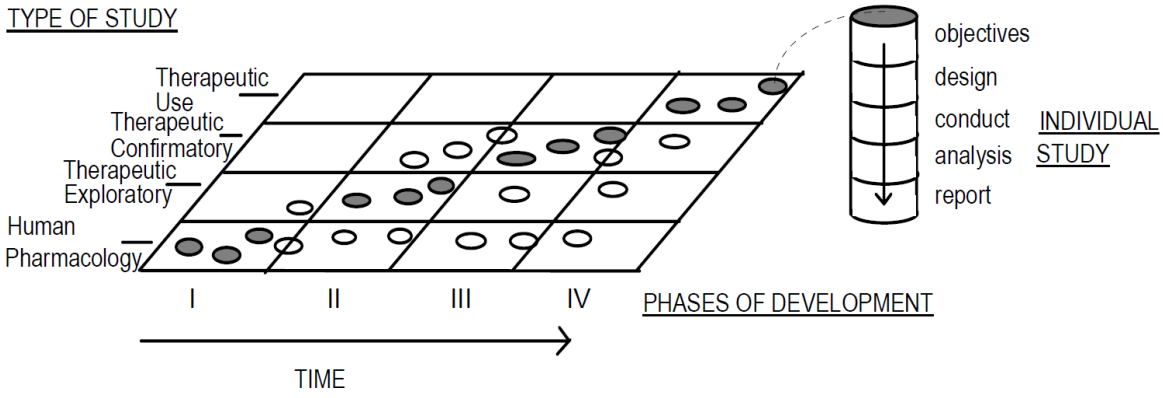

Figure 3 – Correlation between development phases and types of studies.
The filled circles represent clinical trials that more frequently occur at that phase, as reflected in the figure, for example, human pharmacology trials most frequently occur at phase I, and so on. However, human pharmacology studies may also occur at any of the other phases. (Reproduced from figure 1 of (10).)

Observational studies

I devoted my work mostly to clinical trials, however, observational studies are also an important part of a clinical research centre activity.

Observational studies study the causes, preventions and treatments for outcomes and they may be prospective and/or retrospective. In a prospective study, the investigator follows the impact of the exposure going forward in time and wait for the outcome, this is, patients with the exposure of interest are included and they are followed up until occurrence of health outcomes (13). Retrospective studies are based on what have already happened (both exposure and outcome) by looking back at data from records, in other words, patients that already had the outcome event are included, ignoring the effects that happened earlier concerning the exposure and the consequent effects (13). Usually, observational studies are post-market studies performed to collect additional information about that therapy/drug.

Such as clinical trials, observational studies are also classified into different categories. There are 4 main types of observational studies (13):

- Cross-sectional: the patient population included in these type of studies are examined at a single point in time and there is no consideration regarding any changes that may have occurred over time (13). For example:

The study "*Breast feeding and obesity: cross sectional study*" intended to evaluate the impact that breastfeeding have in obesity of children when they start going to school (14). The methodology used was giving a questionnaire to children's parents about early feeding, diet and lifestyle factors. These questionnaires were the "single point in time" evaluation. In this study there is no consideration about the factors that may have influenced that change (i.e. obesity), the relation between breastfeeding will only be measured considering the information given at that moment by the parents.

- Case-control: in this case, the relation between multiple exposures and the outcome is explored (13). Case-control studies are retrospective studies. Investigators rely on records and patients' recalls to understand their exposure and there are 2 groups of patients enrolled: the cases and the controls (13).

As an example, study "*MMR vaccination and pervasive developmental disorders: A case-control study*" was designed to investigate whether measles-mumps-rubella (MMR) vaccination is associated with an increased risk of autism or other pervasive developmental disorders (PDD) (15). Patients with PDD and without this outcome, cases and controls

respectively, were included and assessed for their exposure to the vaccine. In the end, if the exposure of the control and the case group to the vaccine is similar, than there is no relation between the MMR vaccination and the PDD outcome (15).

- Cohort: this type of observational study examines multiple health effects of an exposure based on their follow-up over time to check for outcome occurrence (13). They may be prospective and retrospective (13).

As an example, the study "*Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study*" was developed to evaluate the relationship between the supplementation of vitamin D and the development of type 1 diabetes in the first year of life (16). The subjects enrolled were pregnant women. After giving birth, the babies were monitored during their first year of life for the frequency and dose of vitamin D supplementation. The babies were followed until their adult life (for about 30 years) to evaluate the type 1 diabetes outcome occurrence (16).

- Ecological: this type of studies examines the relationship between exposure and outcome but at a larger scale instead of at individual level (13). This way, investigators may analyse trends in larger groups of people regarding health condition.

As an example, in the ecological study "*An ecological study of the relationship between social and environmental determinants of obesity*", the intention is to evaluate the relationship between the socioeconomic status of a given population and the respective exposure to fast food services (17). The information collected was from a neighbourhood, no individual data was collected, and it consisted in the socioeconomic status and the density of fast food restaurants in that area. The interest is on the observation of the trend that this context may represent: if the exposure to fast food could pose as a greater risk for obesity in lower-income neighbourhoods (13).

Clinical investigation legal and ethical context

Clinical investigation is a highly regulated area throughout the world. I will mention the main European and national legal and ethical context, because it is intrinsically connected, not only in Portugal, but in the other European Union (EU) countries as well.
The European Commission (EC) issues Directives that are transposed to national laws, this is applicable for EU Member States (MS) and, on a voluntary basis, for additional countries that are part of the European Economic Area (EEA) (8). On the other hand, Regulations are typically issued by the many agencies of the EU and must be of immediate implementation in all MS (8). Guidelines represent technical interpretations of the laws about what Regulatory Authorities (RA) would find acceptable (8).
One of the aims of directives, regulations and guidelines is to increasingly harmonize the clinical investigation process.
MS in the EU operated differently in what regards to conduct and approval of clinical trials (11). In May 2001, "The EU Clinical Trials Directive", Directive 2001/20/CE, was formally adopted. It relies "*on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*" (18). The objective is to harmonize the investigational procedure and make clinical trials performed in different countries acceptable for all MS. As MS would still have different ways to interpret and implement this Directive, on 16 April 2014, the new EU Regulation No 536/2014 was issued, annulling Directive 2001/20/EC (19). The Regulation entered into force on 16 June 2014 but will apply no earlier than 28 May 2016 (19). It was issued in the legal form of Regulation to make sure that the rules for conducting clinical trials are identical in all EU (20). Some of the main points of this new regulation are the creation of an EU portal, through which sponsors may submit clinical trials, a single entry point; more transparency of data from clinical trials and simpler rules on safety reporting (20).
European regulations and guidelines that cover many areas related to clinical trials, are available in 10 different volumes of Eudralex. Eudralex represents a collection of "The Rules Governing Medicinal Products in the European Union" (8). Volume 10 is dedicated, specifically, to clinical trials.
The intent to globalize the market was growing, especially for innovative medicines, because the different requirements from the different geographic regions caused the delay

of the process due to duplication of clinical trials. This would consequently lead to waste of human resources that mean waste of money invested. The ICH project (8) was firstly created in 1990 but the need of such project was already reflected in 1980 (21). ICH aims to make recommendations that lead to global harmonization and that are acceptable by RAs in Europe, Japan and USA, the 3 regions involved in this project. The guidelines from ICH are divided into 4 categories in order to facilitate the search of specific guidance: Safety, Quality, Efficacy and Multidisciplinary. Although ICH guidelines are very useful, they are not mandatory to be followed.

Independently of where they are conducted, clinical trials that are meant to be included in a Marketing Authorization (MA) for medicines of human use in the EEA, must be carried out in accordance with Directive 2001/20/CE, in the near future it will be Regulation No 536/2014, and with ethical principles, namely, international Good Clinical Practices (GCP) and Declaration of Helsinki (19).

All proposed clinical trials to be performed in Europe have to be submitted to an Ethics Committee and must obtain a favorable opinion in order to initiate (8). The declaration of Helsinki was first created in 1964 by the World Medical Association (WMA) and has been suffering amendments in order to fulfil its purpose: be a statement of ethical principles to be met when doing research in human subjects. The latest version is from 2013 (22). This declaration includes important human research ethics codes of practice but it does not represent a legally binding instrument in international law (23).

ICH GCP guideline E6 is a document, published in 1996, that describes the responsibilities and expectation from the main involved parties in a clinical trial conduct, namely: investigators, CRAs, sponsors and Ethics Committees (24). It also explains how monitoring, reporting and archiving of clinical trials should be conducted (24). This document takes into account that the patient is the most important intervenient of clinical trials, explaining that the rights, safety and well-being of trials' subjects should prevail over the interests of science and society (25). This became the leader guideline for the conduct of clinical trials, it allows globalization of industry-sponsored clinical research, because clinical data collected in compliance with ICH GCP from one region can now be used to submit drug applications in other regions (23).

In Portugal, clinical investigation is regulated by law No 21/2014, from 16th April 2014 and transposes Directive 2001/20/CE (26). This new law is very broad, because it

encompasses clinical trials, clinical studies (with medical devices) and observational studies. If a clinical trial, observational study or clinical study is to be conducted in Portugal, it should obey to this law.

Statistics of clinical trials in Portugal

Pharmaceutical companies represent the main investors in clinical investigation and companies are very selective regarding countries and sites for conduct of clinical trials (27). This selection is an internationally competitive process which is conditioned by attractiveness factors that the countries demonstrate to multinational companies (27). The following figure shows the number of clinical trials submitted in Portugal since 2006 until 2014. In 2014, INFARMED received 127 submissions for clinical trials approval, from which 119 were, in fact, approved while 3 were refused.

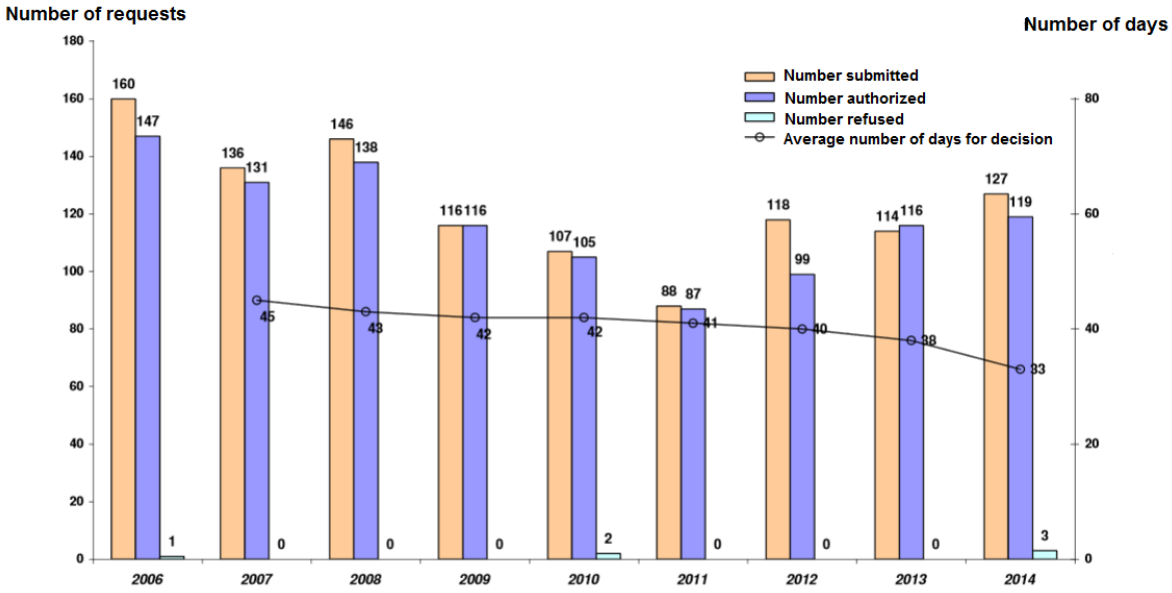

Figure 4 – Clinical research authorization application - statistics by INFARMED.
Numbers of clinical trials submitted, authorized and deferred. The line represents the number of days, in average, that the RA took to make a decision (Adapted from (28).)

Figure 4 shows a decline of the number of clinical trials in Portugal from 2006 until 2011. From that year on, there has been a slight increase, however, not enough to reach the higher number that was achieved in 2006 (147 approved clinical trials).

This poses the question: what is wrong with the Portuguese context that makes it less attractive for pharmaceutical companies? A study about clinical trials in Portugal, based on interviews to people and companies involved in this area, was performed by *PricewaterhouseCoopers* and *Associação Portuguesa da Indústria Farmacêutica* (Portuguese Association of Pharmaceutical Industry) – APIFARMA (29). This study identified the main barriers to the development of clinical research in Portugal. Some of which were:

- Lack of recognition of the potential of investigation to the improvement of healthcare and national economy;
- Lack of regulatory structure adapted to the demands of this activity;
- Negative connotation of clinical trials;
- Little competitive approval deadlines and unavailability of legal approval deadlines, namely of the financial contract and CNPD;
- Depreciation of the strategic potential of clinical investigation by the ABs from hospitals.

Some of the above mentioned barriers are now being addressed by the new Portuguese legislation. It defines deadlines for approval of clinical trials by CNPD and approval of financial contracts by the ABs and reduces the timelines for approval of clinical trials by INFARMED and *Comissão de Ética para a Investigação Clínica* (Ethics Committee for Clinical Research) – CEIC. In Figure 4 it is possible to observe, already, an improvement of the average number of days for approval of clinical trials by INFARMED. This is a good beginning for the establishment of a regulatory structure and the new European regulation will also help in this matter to change the current state of clinical research in Portugal, as well as in other countries.

2.2 Clinical research implementation

Clinical trials and observational studies in clinical research centers

Now that I've explained what clinical trials and observational studies are, in which legal and ethical context they are included and what is the current reality of clinical trials in Portugal, it's now time to explain the course of clinical trials and observational studies when they are to be implemented in a clinical research center.
Clinical trials and observational studies develop along a process that comprehends several steps. Through the perspective of a clinical research center, these phases may be summarized as in Figure 5. This process is common for clinical trials and observational studies, not only in Portugal, but worldwide.

Figure 5 – **Main phases of implementation of a study in a clinical research site.**
Chronologic presentation of the phases of implementation of clinical trials and observational studies in a study site. Observational studies usually have qualification phone calls and not in person qualification visits.

When a clinical trial is to be initiated, the sponsor starts by identifying the countries and the respective potential centers where it may be implemented later. The sponsor is an institution, a company or an organization that is responsible for the clinical trial in its' integrity, namely: initiation, management and/or financing (25). The sponsor may contract services from other people or organizations to perform one or more of the sponsor's functions and responsibilities on the trial, these are called Contract Research Organizations (CRO) (25).

Feasibility phase

For each of the potential sites, the proposal of the study is sent along with a feasibility questionnaire, which is answered by the interested principal investigator (PI) or the designated person. The clinical trial site is the physical location where the trial-related activities will actually take place and where a principal investigator is designated to be the responsible person for the trial conduct at the site (25). Usually, the principal investigator is a medical doctor that is responsible for the participants' health during the study. The feasibility questionnaire intends to capture the main characteristics of the site that will be necessary for the conduct of the trial, including recruitment capability, clinical practice, experience of the principal investigator, approval timings, among other questions. When all the answered feasibilities are received by the sponsor, these questionnaires will then be evaluated by the sponsor in order to choose those clinical research centers with the best characteristics. Some factors that are considered for site selection are referred in Figure 6.

Figure 6 – Sponsor's criteria for clinical research centres' selection.
Factors taken into account by sponsors when choosing the clinical research centres in which to implement clinical trials/observational studies (Adapted from figure 1 of (30).)

The next step is the site selection for the qualification visit. After responding to the feasibility questionnaire and sending it to the sponsor representative, sites wait for an answer from the sponsor with a positive or negative feedback. If the site does not present the adequate conditions to implement the study, the process ends here, but if it is selected as a potential site to participate, the site moves forward in this process.

Qualification visit

After analysis of feasibilities, a sponsor representative does a qualification visit at the sites that had good characteristics. The sponsor representative is usually a CRA, who is responsible for overseeing the progress of the clinical trial and make sure it is conducted, recorded and reported according to the protocol, GCP and the applicable regulations (25). The objective of this visit is the same as a feasibility questionnaire, however, the CRA have the chance to personally evaluate the interest and the conditions of that site to conduct that clinical trial/observational study and also to get to know the team that will be involved in the trial. The clinical trial is conducted by a principal investigator at the site, but he/she can delegate his/her responsibilities to a team of individuals, composing an investigation team. When it is possible, a representative of each department from that hospital potentially involved in the study is present in the qualification visit, because this way doubts can be clarified and possible restrictions may be presented to the CRA so that he/she may clarify the question with the sponsor.
When referring to observational studies, the qualification visit is frequently substituted by e phone call with the interested investigator. The necessary conditions of a site to receive an observational study are not as demanding as for receiving a clinical trial, reason why the qualification visit may be performed by phone.
Then, the sites wait for the sponsor's feedback once again. If the feedback is negative, the process finishes here, if not, the process moves forward to the clinical trial/observational study submission.

Submission phase

Submission is the step that is more specific of Portugal, because each country has its own specificities. To conduct a clinical trial in Portugal, the sponsor must submit the clinical trial's information to the RA and the Ethics Committee. In Portugal, the RA is INFARMED, and the Ethics Committee is CEIC. In order for a clinical trial to take place in Portugal, it must obtain the approval from INFARMED and a favorable opinion from CEIC. Also, CNPD must give its approval. Each of these authorities have defined the documents that must be submitted and that will be revised by each of them. Figure 7 shows, in a schematic way, the approval process in Portugal and the involved organizations. European Database (EudraCT) contains every clinical trials of the EU that

were submitted to the Ethics Committee and RA since the 1st May of 2004 (31). Before submission to INFARMED and CEIC, every clinical trial should be registered in EudraCT database and obtain the EudraCT number.

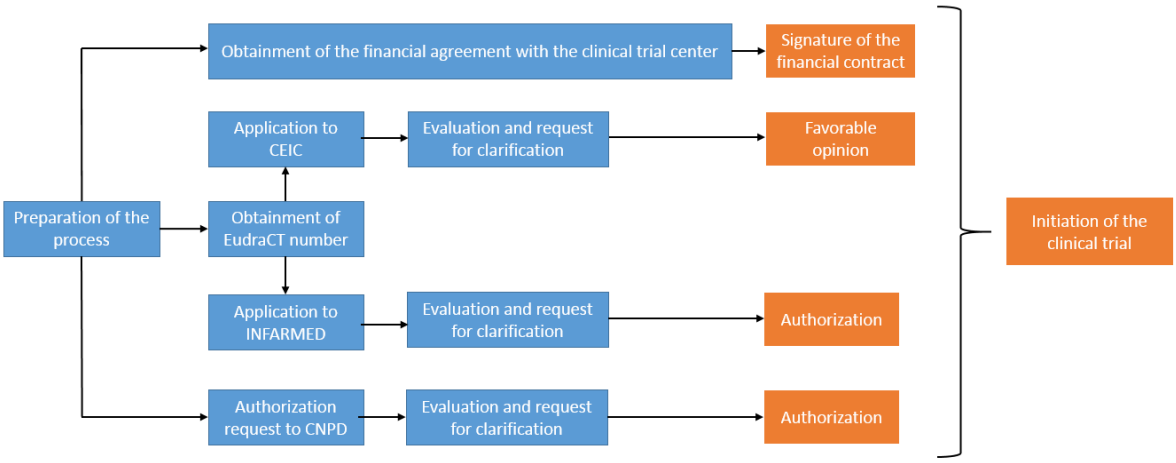

Figure 7 – Approval process of a clinical trial in Portugal.
In the blue rectangles are represented the processes required to gather all the necessary conditions (orange rectangles) for the beginning of the clinical trial (Adapted from (29).)

Submission to the different entities may be performed in parallel, as suggested in Figure 7. The submission of the clinical trial to sites' AB may also be performed in parallel; however sponsors must compromise that the trial will not be started until every approval is obtained. Through the perspective of a clinical research center, submission of a clinical trial requires the collection of several documents and, the most important: the financial contract. This contract is signed by the sponsor, the principal investigator of that site, and finally by the AB when the clinical trial is being approved for conduct in that hospital.
As far as observational studies, they are not submitted to INFARMED, but must be submitted to the *Comissão de Ética para a Saúde* (Ethics Committee for Health) – CES, which is usually part of the site where it is to be conducted in, and to CNPD for approval (32).
When applicable, once the favorable opinion from the Ethics Committee is obtained, the approvals from INFARMED and CNPD are achieved, the AB has approved the financial contract and all the logistics is guaranteed for the initiation of the study, it may begin to be implemented in the clinical research center.

Initiation visit

The start of a clinical trial or an observational study in a site is set by an initiation visit, where every member of the study team is gathered for a more detailed presentation of the clinical trial/observational study, more focused on each member of the team in order for everyone to know what their responsibilities will be on that trial. The dynamics of this visit is very similar to a qualification visit, because it is the sponsor's representative, CRA, who does the presentation of the study to the investigation team. The members of the team should all be present in order to clarify any questions regarding the study that is about to initiate. In this visit there are some documents that need to be filled, namely the training log, which document the training provided during the initiation visit, and the delegation log, which contains the team members, their role and responsibilities, respectively.

Study development

When the study begins and its development phase is set, it starts with a recruitment stage, where patients are included to be a part of the protocol. In general the recruitment period does not end for several months, but depending on the worldwide recruitment and on the sponsor's objectives for recruitment, this period may be shortened or prolonged. When the recruitment period ends, it is not possible to include any more new patients and the ones that have been included continue to be followed according to the protocol defined visits, which depending on each protocol may take months or years. From the moment patients start participating in the study until their last visit is the phase where data are collected. Data are collected in medical records and then filled in on-line platforms, called Case Report Forms (CRF). According to what is defined in the protocol, the CRA visits each clinical research center in defined time points in order to check if the study is being conducted in compliance with the protocol, the regulatory requirements and GCP. CRAs check medical records in parallel with CRF to see if data is in accordance to what has been registered.
In the end, when every patient included has finished the follow-up phase, it is time to finish the data collection and correct any errors in the database so it may be closed and data may be analyzed.

Close-out visit

The final phase of a clinical trial in a site is the close-out visit, when the CRA checks for the last time that every dossier is complete and updated, when the materials provided by the sponsor are collected and the final statements regarding the filing of the dossiers are made. After this, the study dossiers must be kept safe in the clinical research center for the time period defined by the sponsor and specific regulatory requirements. If any information regarding the study is requested by the sponsor, the RA or the Ethics Committee, then records should be made available.

3. On-the-Job Training

In chapter 3, I intend to focus on the activities performed during my curricular internship and present what I have learnt and the experience I gained. I have started my curricular internship on the 1st of July 2014 until the end of April 2015. My route within Blueclinical was not limited to the experience in CHVNG/E, I also had the opportunity to develop activities in Blueclinical back-office. Considering this, I will begin with the description of the activities developed during the time I was in the back-office and, then, I will focus on the description of the activities as a CRC in CHVNG/E.

3.1 Blueclinical back-office experience

On the 1st of July 2014, I started developing functions of quality management at Blueclinical headquarters. I revised every Standard Operating Procedure (SOP) related to CRP practices, which were already elaborated, and I have presented some suggestions of improvement. Then, I was instructed to elaborate flow diagrams for each of the SOPs in cooperation with a colleague. After revising the SOPs and drawing flow diagrams, I and my colleague have compared our work and we concluded the flow diagrams were not useful for the reading of the SOPs, which is the main purpose of the existence of flow diagrams. We presented our work and conclusions to the Clinical Operations Director (COD) and the flow diagrams and the conclusions drawn were considered.

I was, also, involved in the creation of a document for the control of protocol visits from each partner hospital. That was a Microsoft Excel document with the information of every hospital of Blueclinical CRP, which contained the necessary information to identify the protocol, the hospital where it was being conducted, the visits performed and the ones predicted to be performed by each included patient and the profits for each visit. This document would allow back-office to control the activity of each hospital and make a prediction of future profits for the company. This document took several weeks to complete, because I had to check and update the activity of each hospital, sometimes data was not in accordance with the previsions that were possible to make from this document and I needed to call or send e-mails to the CRC allocated to each hospital and ask the

questions raised by this data analysis. After all the corrections were made, the document was passed to another colleague in order to implement some improvements.

The last project I had before leaving Blueclinical headquarters and sometime, still, after starting at CHVNG/E, was project management activities from 2 different projects, where I gave support to the project manager. I was present in meetings where the project manager would present the project, explain who the involved parties were and state what was the status of the project at that time. In these activities, I had the opportunity to view clinical trials from another perspective, because I helped in the submission of clinical trials to the authorities (INFARMED, CEIC and CNPD) and to the clinical trial centers involved, so I had to prepare documents for submission, translate documents related to the clinical trial and contact the clinical research centers involved. I never contacted any other involved party, but I was copied in every e-mail that was exchanged, which allowed me to accompany the development of the process.

The activities mentioned above were the leading tasks performed during the stay at back-office, but I have been involved in other activities, such as preparation of Blueshare, which is a kind of poster done every month containing news from the different business areas of Blueclinical; I was involved in the elaboration of 2 Blueshares (July and August). I also attended to one meeting of medical writing and, mostly, I helped my colleagues with what they had to do. For example, I helped in the elaboration of a document, which contained a list of required documents and requirements from INFARMED, CEIC and CNPD for submission of new clinical trial requests, for this I searched on the websites from each of these authorities and I have discovered they have available a list of documents and the required organization for the submission of new clinical trials proposals. I helped with the updating of the activity map referring to CRP hospitals, sometimes CRCs from partner hospitals forget to update the back-office with the new protocol visits and procedures that took place, so I called or e-mailed the CRCs to make sure the information was updated and when I obtained the answers I would update the activity map document.

3.2 CRC experience

On the 11th September 2014, I have started to play CRC functions at CHVNG/E. I intend to describe the developed activities in a sequential manner in order to provide a chronologic view of what happens in a clinical trial site on a CRC point of view.
I have decided to split the CRC functions I performed into 3 different phases: pre-approval, post-approval and continuous activities. In general, my main responsibilities as a CRC during the internship, in an initial phase, were the following:

- Cooperation in obtaining answers to feasibility questionnaires within the agreed timelines;
- Elaborate/adapt documents for the submission process to the competent authorities and AB of the hospital;
- Assist on the submission of clinical trials and observational studies to the hospital's CES and/or AB, where applicable.

During the clinical trial or observational study development in the site, I had to make sure the ethical principles and applicable regulations were met and that it was conducted in accordance with the protocol. The following functions were the ones I assumed during the development phase of the clinical trial/observational study:

- Support the investigator in the selection of potential participants for the study;
- Guarantee that the well-being, rights and confidentiality of the participants are protected;
- Help the investigator on the planning of the protocol visits, including everything that is behind it;
- Support monitoring visits, managing in advance for the presence of the necessary staff, for example, the PI;
- Fill electronic or paper CRF correctly and accurately in accordance with the information provided by the investigator.

When the clinical trial/observational study reaches the end, the main functions consist in maintaining the records duly archived, in accordance with the sponsor's indications and make these records available when requested by the sponsor or competent authorities.

During the internship I had the opportunity to gain experience with different types of trials for different types of conditions. In Table 2, I present the number and target pathology of clinical trials that I have coordinated as a CRC.

Table 2 – Clinical trials in which I was involved as a CRC.

Number of clinical trials	Therapeutic area
1	Lung cancer
3	Diabetes
1	Chronic obstructive pulmonary disease
1	Non-cystic fibrosis bronchiectasis
1	Rheumatoid arthritis

I also had some experience with observational studies, although I did not dedicate as much time to them. Table 3 is similar to Table 2, but refers to observational studies I was involved in.

Table 3 – Observational studies in which I was involved as a CRC.

Number of observational studies	Therapeutic area
1	Heart failure
1	Atrial fibrillation

3.2.1 Pre-approval activities

Before a clinical trial starts in a clinical research center, there is a big amount of work to do until the site is ready to receive the clinical trial. With observational studies it is not such a laborious work, because the intention is that they are more close to normal clinical practice.

Feasibility phase

First of all, it starts with the arrival of a new clinical trial or observational study proposal. It is usually received by e-mail and it can come from 3 possible different sources:

- The sponsor
- The CRO
- Blueclinical back-office

If the sponsor/CRO is the sender of the new proposal, it is sent to the doctor, directly, or to GIC. If it is sent directly to the doctor, he/she is, most of the times, the one that will be the PI of the clinical trial. When it is sent to GIC, we evaluate to which department that investigation applies and send the proposal to the service director. Then, the person who will be the PI is decided among the doctors from that service and when a decision is made, it is communicated to GIC so that we can communicate to the sponsor/CRO.
When the proposal is sent to GIC by Blueclinical back-office, I send the proposal to the director of the service where the clinical trial is applicable and the process described above is triggered. Sometimes, when we already know by experience with a service that the interested doctor is always the same, we send the new proposal directly to that doctor. In general, our first approach to contact is always e-mail and then we do phone or in-person contact.
When the e-mail is sent, it contains some information about the clinical trial that can be the protocol synopsis or a very brief summary of the study information, a feasibility questionnaire and a Confidential Disclosure Agreement (CDA). Sometimes the CDA is sent before anything else and it must be sent signed and dated by the interested doctor in order to receive more information regarding the clinical trial. For observational studies the approach is the same.

The feasibility may be a questionnaire on paper, answered by hand, scanned and sent to the sponsor/CRO, or it may be a questionnaire online that is submitted when answered and the sponsor/CRO can then access that information. Since doctors are always very busy, part of my job is to facilitate every necessary task. In order to be more practical, I print the questionnaire, even if it is an online questionnaire, and take it personally to the interested doctor. I also study the information about the protocol, so I can explain verbally what that proposal consists in, and read the feasibility questionnaire so that I can clarify promptly any doubt about any of the questions. If I am able to answer any of the questions, I do it before presenting the questionnaire to the doctor; questions such as approval timelines, hospital's logistics and equipment, name, e-mail, fax number and other information about the investigator that we have if we have worked with that doctor before, among other information that is possible for me to answer. The doctor then focuses on the medical, such as numbers of patients and clinical practice treatments. A very important question in this phase is the number of patients that the investigator considers possible to recruit within a specific time. The answer given to this question is important if the site is selected for participation, because it is the basis for discussion about the commitment of recruitment of our site.

Once the CDA is signed and dated and the feasibility questionnaire is duly answered, I send this information back from where I received it. If it was received from the Blueclinical back-office, I send it back so they may forward it to the sponsor/CRO, unless I have other instructions. When I receive a new clinical trial or observational study proposal that did not came from the back-office, I must notify them, especially if the feasibility questionnaire is answered and sent to the sponsor/CRO. In the back-office there is a "feasibility tracking" document that keeps track about the feasibilities that are answered from each hospital of the CRP. This document must be kept up to date, because there are many new proposals and if this information is not controlled we lose track of the feasibility questionnaires that are answered.

When the sponsor/CRO has all the information, we have to wait for some answer regarding the selection of the site. This waiting may many weeks and sometimes we do not receive any answer. When the feedback is positive and the site is selected to be one of the possible sites participating in the study, the sponsor/CRO representative – CRA – shows

willingness to schedule a qualification visit through e-mail or phone contact and this is the phase when I start arranging this meeting.

Qualification visit

At this point, I analyze the protocol and conclude which departments should be involved in order to fulfill the protocol requirements. Every clinical trial involves medication, which means the intervention of the hospital's pharmacy; most clinical trials involve blood samples or samples from other nature, which need to be processed and sent to central laboratories, the processing of the samples requires a local laboratory intervention. Central laboratories are laboratories contracted by the sponsor in order to analyze the samples from the clinical trial patients. Following this logic, in the qualification visit should be present a representative from each of these departments. What I do, is evaluate the availability of the staff from each department and evaluate their interest in being part of a clinical trial, then I try to arrange a date suitable for all team members to be present at the qualification visit. For observational studies, the PI, sub-investigators and CRC are enough, because there is no need for involvement of other departments.

When a consensus regarding the date of the visit is reached, I confirm to everyone that confirmed their presence the day, time and place where the qualification visit will be held. In this visit, the CRA, a representative of the sponsor or CRO, is usually the person that leads the visit. The CRA presents the clinical trial to the team, discusses the inclusion and exclusion criteria with the investigators, evaluates the site capability of recruitment through the forecast of the investigators, and tries to understand how the trial would be conducted in that site, which are the constraints and how it may be resolved.

All the equipment that is used within the scope of a clinical trial must be calibrated and the certification of the calibration must be available. This is the phase where the CRA questions if the materials are calibrated and if there are available certification; if the freezers and refrigerators where the blood samples are stored and for storage of the trial medication have temperature data loggers; if the team has GCP training and if they have updated *Curriculum Vitae* (CV); when the local laboratory is required to perform any analysis, it must provide the normal ranges for the parameters required by the protocol; where the clinical trial materials, including dossiers, are to be stored, among other conditions. When it is possible, the CRA visits the departments where clinical trial

activities will be developed. For example, during the qualification visit for a clinical trial on ophthalmologic pathology, the CRA went to visit the rooms with the equipment where the exams would take place. Observational studies require that the team has GCP training and updated CV, and that the used equipment is calibrated, when applicable, however, other demanding requirements are not applicable.
Since the beginning of my internship I have attended to many qualification visits from different sponsors and CROs, both from sponsors that did not select our site and from sponsors that now have trials being conducted in CHVNG/E. I never had the chance to attend to qualification phone calls for observational studies, because they were only performed between the CRA and the PI and there was no need for my presence.
After the qualification visit, we have to wait for the sponsor's feedback. When it is positive, the site is selected to participate in the trial and we start the submission process that begins with the preparation of documents and negotiation of contracts that will be used for submission to the AB of the hospital. This selection information is usually provided by e-mail, directly from the sponsor or by the CRA, or by a phone call from the CRA when the objective is to accelerate the submission process, however, this is always officially confirmed by an e-mail.

Investigator Meetings

For most of the clinical trials and observational studies there is the possibility to attend an Investigator Meeting (IM). During the internship I had the possibility to attend to 4 IMs: the first was in Lisbon, Portugal, for an observational study in patients with urticaria; the second was in Budapest, Hungary, for a clinical trial in patients with HIV; the third in Paris, France, for a clinical trial that intends to investigate the secondary prevention of stroke and systemic embolism in patients with a recent embolic stroke of undetermined source; the last one was in Istanbul, Turkey, for a clinical trial in patients with symptomatic pulmonary hypertension.
For observational studies these meetings are performed in Portugal, if it is a national study, or by online conference if it is an international study. During my internship I did not have the chance to be present at any online IM.
In these in-person meetings, I had the opportunity to hear the presentation of the protocol details from the people involved in the design of the trial and get to know different realities

from sites around the world. Also, I had the opportunity to get to know investigators, study coordinators, nurses, technicians and pharmacists from other Portuguese sites. I consider that attending to IMs is a very useful tool to understand the protocol, because I felt I was more aware of protocol details from these studies than from others, which I was not present in the IM. However, travels and time differences are very tiring and sometimes I could not take advantage of the meeting as I would wish. All of the IMs I attended occurred before submission of the dossier to the AB of the hospital, which was useful because I could study the protocol before it started in CHVNG/E, however, sometimes the IMs occur long before it's beginning and by the time of the initiation visit we do not remember a lot about the study.

Submission phase

Table 4 states the template documents we have in CHVNG/E to provide to sponsors or adapt in order to be part of the submission dossier for a clinical trial/observational study site:

Table 4 – Template documents needed for submission to the AB of CHVNG/E.

Document	Content	Signatures
Authorization application letter to the AB	Letter written in Portuguese asking permission to conduct the clinical trial/observational study in that site. This letter also contains a summary of the most relevant aspects of the study to the site. The template text provided should be adapted to the letter model from the sponsor.	Sponsor or sponsor's representative.
Sponsor statement	Letter containing the status of approval of the trial by INFARMED, CEIC and CNPD and statement that the sponsor will only initiate the clinical trial/observational study when every approval is gathered. The template text provided should be adapted to the letter model from the sponsor.	Sponsor or sponsor's representative.
Index	Identification of all the documents contained in the dossier. CRC provides template.	Sponsor or sponsor's representative.

Statement of the site conditions	A statement that indicates that the site possesses the adequate conditions regarding equipment, facilities and human resources, to conduct the trial. Written in Portuguese.	Head of the involved departments of the hospital and PI.
Recruitment Modality	Document stating by which means patients will be identified and that recruitment will only be performed by the investigators. Written in Portuguese.	Signed by the PI.
Participants' compensation	Statement referring that participants will only be paid by the protocol incurred expenses and will not be compensated by any other mean. Written in Portuguese.	Signed by the PI.
Principal investigator CV	A CV stating the PI's experience in clinical trials/observational studies, professional experience, GCP training and any other relevant information for the matter. Prepared in English from an available template.	Signed and dated by the PI.
Investigational product circuit	A document that defines who is responsible for supply, reception, storage, prescription, preparation, dispensing, information, administration, devolution of the product to the pharmacy of the hospital and the sponsor and destruction of the investigational product.	Person preparing and confirming the information on the document (usually pharmacist and CRA).
Pharmaceutical service statement of conditions	Statement that the pharmaceutical services possess the right conditions for the investigational medicine. This template belongs to the pharmacy, we do not have access to it.	Head of the pharmacy department.

For observational studies there are some differences regarding the necessary documents for submission. Since observational studies must also be evaluated by CHVNG/E's CES, there must also be available an authorization application letter to CES, which is very similar to the authorization application letter to the AB. In this case, any document related to pharmacy and trial medication is not applicable.

In this phase, the PI must define the final team that will be part of the study, this information is important, because I need to know the study team to include in the documents to be prepared for the submission and to include in the financial contract. When arranging for submission, I prepare the necessary documents and go collect personally each of the necessary signatures.

During the process of preparation and signature of the documents, the financial contract is being negotiated. In Blueclinical, we have a person that is responsible for this, so when the sponsor/CRO wants to start negotiating the contract I give my colleague's contact and they communicate from then on. However, this is not a process my colleague can finish on her own. She is not present in the site, so my support is essential, because I tell her the team constitution, the distribution of founds that the PI establishes and other information from the investigation team when is needed to include in the contract. In the end, the sponsor/CRO prints 3 copies of the financial contract (one for the PI, other for the AB from CHVNG/E and another for the sponsor), which arrive to CHVNG/E within the submission dossier. Once I receive them, they are already signed, dated and initialed by the sponsor or CRO, then, I collect signature, date and initials from the PI before submission. The AB's director will find a field for signature and date and every page must be initialed. The CV from the PI is also a very important document we need to collect. Usually, doctors have extensive CVs with all the information from the beginning of university until that moment.

We have a CV template which contains the most important information for the purpose. In order to help doctors and to create a CV that can be used for future studies, I adapt the complete CV they have into that template and print it to collect date and signature of this document. The PI's CV is the first that is needed, but the CV from every member of the team needs to be collected and archived in the Investigator Site File (ISF). An ISF is a set of dossiers that contains all the information the site staff may need to conduct the clinical trial in accordance with the protocol, GCP and regulatory requirements. I save every CV from every person participating in studies, because it may be needed in the future. In order to be part of an investigation team, one should have the GCP training performed and the certificate available. This is a train that is performed online. When it's needed, I help with this task trying to explain in a simpler manner what is taught in the training.

There are other documents that need to be signed and sent to the sponsor during this submission phase, some of them are the following:

- FDA statement of investigator, which states that the investigator will comply with FDA regulations related to the conduct of the trial;
- Financial Disclosure Agreements, in which the investigator state that there are no financial interests involved;
- Protocol signature page, every time a new version from the protocol is approved, the investigator must sign the signature page, this applies not only for the submission phase but also for all the development phase of the study;
- Acknowledgement of receipt of the protocol, investigator brochure and other documents and materials sent by the sponsor to the site.

When the submission documents are ready, the sponsor sends the submission dossier to the site, directly to GIC, so that we may submit it to the AB, if it is a clinical trial, or to the CES first and then to the AB, if it is an observational study. When I receive the submission dossier, I place the original documents in the duly place of the dossier (declaration of site conditions, recruitment modality, participants' compensation and investigational product circuit). Then, the dossier is reviewed to make sure every essential document is in the dossier. When submitting the dossier, I prepare 3 different documents to go with it: a letter, from GIC, directed to the AB's chairman, a summary of financial analysis of the financial contract and an internal mail to document that the AB received the dossier. I have not done many submissions, because I was not very experienced in the submission process and I had a colleague who assumed responsibility for this task, however, I always helped in the preparation of documents for submission. When my colleague was not present, I had to replace her and did submission of 2 dossiers from 2 clinical trials on my own.

Training and platforms access

As the initiation of the trial is getting closer, there are more tasks to complete. Every member of the team has to do online trainings related to the protocol.
In order to have access to the different platforms from the trial, first it is needed to register and then do the training. In the end, usually there is an evaluation questionnaire, which should be passed in order to obtain the certificate and gain access to the platform. The accesses that I had for the clinical trials where I participated in are:

- Training platforms, where the only thing that is to be done is trainings and print certificates;
- CRF, in which the data collected from the Electronic Medical Records (EMR) from each visit are introduced;
- Interactive Web Response System (IWRS), which is a system through which I declare the patient was included in the trial, the medication kits are attributed randomly to a subject and I declare the patient has ended the participation in the trial.

Each of these platforms is accessed through the use of a username, which may be the e-mail or a name created automatically, and a password. At first, a default password is sent to access the platform for the first time and, once I log in, I immediately have to change the password. I have access to many platforms from a wide range of clinical trials, so I keep all of my credentials saved on a document protected by password, this way I do not forget them.
For observational studies, the only required access is to the CRF. The trainings are performed in the initiation visit, so the process is a lot simpler than for clinical trials.

Financial contract approval

Depending on the work load of the hospital's AB, it usually takes about 2 to 3 weeks to obtain approval, sometimes it is faster and other times it takes longer. When the submission dossier is returned to GIC, I confirm if it was authorized or not. If it is, I scan the letter where the AB declares the authorization of the trial and the financial contract with the signature of the AB's chairman. Then, I send these scanned documents to the CRA and the PI.

In the cases when the clinical trial is not approved, I communicate to the CRA the reasons why it was not approved, because the justification for refusal is explained in the letter where the declaration of authorization is written. If it is possible to be corrected, we wait for the documents substituting the incorrect ones, replace them in the dossier and submit again.
In this phase, when the financial contract is approved by the AB, we progress in this process of implementation of the study and pass to the post-approval activities.

3.2.2 Post-approval activities

Initiation visit

The next step is to schedule the initiation visit. When the study have every approval and the site is almost ready to start including patients, the CRA sends an e-mail demonstrating willingness to schedule the initiation visit and I send an e-mail to the team to ask for their availability in order to choose a day that is convenient for everyone. This is always a process that takes some time, because the availability of each person is very restricted and it is not easy to arrange a possible date and time to gather everyone. It is important to remember that CRAs also have other scheduled visits in other sites so I also confirm their availability.

When a consensus is reached, the initiation visit is scheduled and we are in the final phase to finish every pending issues for the trial initiation, this means: every online training must be completed and the certificates available, every access to the necessary platforms created, the CVs from every member of the study team updated and signed, calibration certificates from the equipment available and the material that is provided by the sponsor must be in the site (for example, biologic sample kits and respective sipping materials, ECG device, and other materials when applicable). Many of these requirements are not applicable for observational studies, so a site can be ready for an observational study much faster than for a clinical trial.

When the initiation visit takes place, the study team is gathered to receive training from the CRA on the protocol. In this visit, the team has the opportunity to ask questions to the CRA, who may answer and clarify everybody in that moment or ask the sponsor and then clarify the questions that could not be made clear. The CRA presents the protocol and specifies the role of each of the members of the team in the study.

Off course, every information is important for me, as a CRC, however there is some information that I give special attention to during the initiation visit: inclusion and exclusion criteria to help the investigators identifying potential patients; end of recruitment period, because it is until that period that we should recruit the number of patients that we compromised to; the number of patients the site compromised to recruit, because recruitment is the most important part of the entire process; flowchart, in order to

understand what procedures are to be performed in each visit and understand which staff members I will need to coordinate for the good conduct of each visit; get to know all the members of the team, because there are always new people integrating study teams and, since I contact with everyone during the study, it is important to get to know them.
In these visits there are some documents that need to be signed by the people present. These include the delegation log and training log. The delegation log is the document that contains the people that are part of the team, the date they have started their functions and their responsibilities. The training log includes the people that have received training by attending to the visit. Those who were present in the visit do not need to do online training for the protocol, because they were trained in the initiation visit. Those who could not attend need to do these trainings and provide the certificate as soon as possible or need to receive training by a member of the team who has been present in the initiation visit. If there is a new member of the team or if that person could not attend the initiation visit, he/she must sign the delegation log and training log before performing any activity related to the study.
If the sponsor compromises to provide any equipment or material it must be sent to the site before its initiation. Sometimes the preparations for activation of the site may delay and the site activation is not possible to be performed immediately after the initiation visit. The CRA knows when the material is sent to the site and I must confirm when new material arrives from each protocol. This material may include: kits with tubes for blood drawing, cups for urine sample, shipping material to send biologic samples to central laboratories, Electrocardiogram (ECG) device, ISF, among others. If the material is not available before the initiation visit, the site cannot start the development phase of the clinical trial until all the required logistics are met. For example, if the biologic sample kits are not available and it is needed to perform blood analysis on the first visit, it is not possible to start including patients right away, otherwise it would be a deviation from the protocol.
I have been in around 6 initiation visits during my internship. These are visits that may take all day, depending on the complexity of the study, and the CRC is a very important part of this visit, because investigators do not have as many time to attend the visit as would be necessary, so, I am the one who should retain most of the information so I can then pass it to investigators and other study team members who could not attend or be present for too long.

In this visit, the CRA brings the ISF, when not sent to the site before the initiation visit. The CRA shows me how it is constituted so I can get to know where to find the information and which documents must be kept updated.
When this visit ends, after all the conditions for initiation are gathered, the site is officially open for recruitment, which means patients may start being included in the protocol. This confirmation is sent by e-mail from the sponsor and the development of the clinical trial may now begin. This may happen immediately after the initiation visit or the site may be considered ready for recruitment sometime after this visit, when all the conditions for initiation are met.

Recruitment of patients

Once the recruitment period is opened, I must understand how I can help with the recruitment. In some trials, the type of patients looked for are followed in the consultation, in other cases the criteria require, for example, patients that are hospitalized and must be identified on their arrival. Regarding all these differences, I must look for strategies to help in the selection of potential patients. The ultimate responsible for the inclusion of patients in protocols are the investigators, so they are the ones that must do the final evaluation before the inclusion of the patient.
The developed strategies I had the opportunity to practice were basically revision of patients' processes and group meetings. On the beginning of my internship I attended group meetings from oncologic pneumology department. In these meetings, doctors discuss patients when they do not know which next step should be taken. In the beginning, I was present during most of the meeting, but then it revealed to be unproductive, because doctors know their patients and do not tell every information we need to know in order to identify if the patient meets the inclusion and exclusion criteria. Then, we started to check the processes of each patient that was going to be discussed before the group meeting and we would attach a document to the process which contained the criteria we had into account to identify that patient. The rest of the criteria had to be checked by the investigators, because we are not doctors and do not have the capabilities to do this evaluation. After this, I would go to the group meeting closer to its' end, because the objective was to know if any of the patients identified in the revision of processes could be included in the trial. Sometimes they may also identify patients that we did not consider as

potential. This activity would remind the investigators to keep in mind the inclusion and exclusion criteria.

The meetings were performed every week, on Monday. I would review the processes on Friday and leave the written evaluation attached to the respective process.

In another case, I had access to the consultations some investigators from a clinical trial in diabetes had the next week. I would review the electronic records from each of the patients who would be in the consultation for the next week and would make a list of potential patients identified by me. Right before the beginning of the consultations, I would deliver this list personally to the investigator. First, my presence would automatically remind them of the need to recruit and second, with the list of potential patients, it would narrow the window of possibilities and allow them to evaluate only those cases instead of checking inclusion and exclusion criteria for every patient of their consultation.

This is an adaptive process, which means that each investigator has a different way to work, some react very well to our help in regards to search for potential patients, others face it as an intrusion to their work and prefer to select patients on their own and not be pushed to do so.

When patients are identified, it is time to propose the clinical trial and see if they want to participate or not. In this phase, the investigators contact me informing of the intention to schedule a visit for a patient they intend to include in the protocol.

The proposal is based on the oral presentation of the context of the clinical trial and also a written document with the description of every aspects a patient should know before accepting or declining the participation. The patient is given time to decide and sometimes the decision is not made on the consultation, it is postponed for about a week later and then, if the patient accepts to participate, we do the screening visit. I always reinforce the fact that they do not have to accept, because if they do not want to participate there will be no penalties and they will be given the best care for their specific case.

During my experience I have dealt with, broadly speaking, 2 types of patients: those who completely trust the doctor judgement and the ones that are always apprehensive, not only because they are participating in a clinical trial, but with any new decision regarding their treatment. In the first case, when the investigator proposes the trial, the patient immediately accepts and justifies it by saying “if the doctor thinks this is the best option for me, then of course I will accept”. The second case of patients are always worried about switching the

treatment they are receiving because “if I am doing so well with this treatment, why should I change it?”. My experience shows me that when patients feel that we understand their position and that we do not intend to force his/her participation, they are a lot more willing to accept and that over the course of the clinical trial, patients become more welcoming to the participation. The way the Informed Consent Form (ICF) is presented makes every difference regarding the reaction of patients. If the investigator talks about the potential benefits for the patient, especially when they talk about safety and efficacy of the product towards the patient’s disease, patients feel a lot more willing to participate. However, investigators should be honest with patients so they know what they will be subjected to and make a conscious and thought decision, because if the reality is different than the explained by the investigator the patient may reject the participation and decide to quit from the trial.

Obtaining informed consent

Once we obtain the approval of participation by a patient, it is time to sign the ICF. This is a very important moment of the whole trial. The patient and the investigator presenting the ICF, sign and date 2 copies of the informed consent, one stays in the dossier containing the documentation of each visit, the other is given to the patient who should save it until the end of the trial. I repeat this process when a new version of the ICF is released, 2 copies are signed and dated by both the patient and the investigator and this is done as soon as this new version is sent to the site. This is a very demanding aspect, because it is the source of some audits’ and inspections’ findings. Unless the patient is not capable of doing so, this document must be signed and dated by the patient himself. Investigators place the date or the patients’ name instead of them in order to be faster and easier for the participant, however, it is a very erroneous thing to do. When I am not present to accompany the visit, I reinforce this aspect and use a lot of post-it notes to try to avoid any mistake from happening.

Visit procedures: clinical trials

The next step is to register the patient on the IWRS system, which will allocate a number to the patient and is performed on the screening visit, after informed consent process. This number will be the identification of the subject for trial purposes and information that is

shared with the sponsor/CROs must never contain the participant identification, only the subjects' number.

The screening period consists on a period of time (days or weeks) used to assess the patients' compliance with the protocol criteria. For those who do not meet all the eligibility criteria for inclusion in the trial after the screening period, the patient must be stated as screening failure which must be registered in the IWRS system. The IWRS will allow the sponsor to know the amount of patients included and the need for investigational medicinal product supply, so its update is very important.

Patients' visits are performed according to the flowchart and the detailed description of the procedures. In general, protocols start with the screening visit, the randomization visit is when they are randomized (start receiving trial treatment) and is usually the second visit, following the treatment period, the end of treatment and end of study visits.

The information from the flowchart is very important for the first phase of any visit: the preparation. Different visits have different procedures, this is why it is very important to prepare the visit, and it is difficult to know by heart the procedures just by looking to a protocol's flowchart few times.

Preparation of visits is crucial for me, because investigators trust my knowledge about the protocol and the requirements for that specific visit. Most of the times, visits are performed in the morning, first because investigators are more available for consultations in this period and, also, because some protocols have requirements that force the visit to be in the morning, for example, the need for the patients to attend the visit fasting. I usually prepare visits the day before they happen. At first, what I did to prepare protocol visits was a checklist of all the procedures, once they had been performed it would be checked. When every topic was performed, all the boxes would be ticked. This was a good way to guide me and investigators on the procedures, however, records did not have good quality, because investigators had to write everything on the EMR and this is something that takes time and concentration, which is not always possible for them during protocol visits. Investigators have to reconcile their normal medical practice with the investigation activity and sometimes they don't have much time to dedicate to the visit. Since this method presented some flaws, I have started elaborating a template text in Microsoft Word for each visit, which contains every activity to be performed per protocol. In clinical investigation, what is not written was not done. The purpose of the template text is to make

sure every activity required per protocol is registered. This text was provided to the investigators, they copied and pasted the text to the EMR and then they only needed to adapt the information obtained in the text. This way, every activity is registered, as required, and doctors know what is needed to do. When I know the patient name and process number, I search in the EMR, to which I have access, and write this template text including, already, the information of that particular patient from the consultations available on the electronic system of the hospital. With this methodology, the records are more accurate, there are fewer findings in the monitoring visits and doctors do not need to spend so long on the visits writing every procedure. Preparation, however, does not come down to registries.

For visits which include blood, urine or other biologic samples, it is necessary to know how these samples are collected and processed, if they will be analyzed in the local laboratory or if they will be sent to central laboratories and, if sent to central laboratory, how samples should be sent (ambient temperature or frozen). When frozen samples need to be sent to central laboratory, I need to order dry ice, so frozen samples can be placed on it and be sent to central laboratory properly packed. Also, the material to use for sample collection is usually provided by the sponsor in individual kits, which are separated by visit, this is, there are kits for visit number 1 and kits for visit number 2, in separate, and so on. I need to verify if there are available kits for the visit in advance, because if kits are missing I need to order more and it takes some time until they arrive to the site. On the visit, I choose the appropriate kit and take it to the nurse room to collect the samples. On each kit, there is a requisition that is to be filled with information regarding the patient and the collection. Beyond this, each collection device (for example the draw tubes, containers for sputum, etc.) must be identified with the subject's number. When the nurse is collecting the sample I place the labels and identify the collection tubes, so when this is taken to the clinical pathology service the team member may know to which patient that sample belongs to. Every tube is identified with a label that contains a barcode, if a tube is wrongly labeled this will create issues when samples are analyzed at the central laboratory. When the flowchart indicates that an examination is required, for example, a spirometry, an echocardiogram, an x-ray or other type of examination, in- or outside the hospital facilities, I need to schedule it in advance so the results may be available on time for the visit.

If any analyses were performed on the last visit, the results must be available so the investigator may check the results. I must make sure that the investigator checks it as soon as possible after the results are sent to the site.

When it is a visit with trial medication dispensing and the last visit medication is to be returned (when applicable), I must use the IWRS system to randomly assign the medication kits to that patient. In my experience, I have to print the IWRS report, where the medication allocated kits are described, and take a prescription form filled by the investigator. Both the documents must be signed and dated by the investigator. When I arrive to the pharmacy I deliver the documents and the medication from last visit (when applicable) and wait for the new medication to take it to the patient. When I receive it from the pharmacist, I must sign the "received by" section from the prescription form.

All of the activities mentioned above require coordination with the study team: for the samples' analysis, I need to notify the nurse and the clinical pathologist that there will be a visit scheduled on a determined day, the nurse needs to collect the blood, urine or other samples, defined by the protocol, and I will be coming to the clinical pathology with the samples in order to be analyzed or processed and sent to central laboratory; to schedule an exam I must talk to the team member that is responsible for performing it and let him/her know when the exam should be scheduled and when the report/results should be available; for medication assignment, the pharmacist must be aware of the visit date in order to be expecting me when I arrive at the pharmacy to collect the medication. For these coordination activities, I may use e-mail, phone calls or in person talk, depending on each person. Some people regularly check their e-mails and quickly answer by confirming the receipt of the e-mail and their availability for that day. This way, the information may be registered in writing and easily accessed when there are any doubts about the date of schedule. Others do not access the e-mail regularly or do not use the e-mail at all, consequently, the communication strategy must change and a phone call or in person talk are the preferable methods. In these cases, I usually elaborate a worksheet to register the visits' dates so it may be registered on paper.

Depending on the trial conditions, there may be other preparations for the visit day, for example, some sponsors make contracts with taxi companies so patients may be driven to the hospital without having to spend money with the travels. In these cases, I must schedule the taxi to pick up the patient on the visit day, at the most convenient hour.

During the visit I accompany the patient to where he/she needs to go, namely, go to the nurses, go to another department to perform an exam, if there are quality of life questionnaires to do for that visit I am usually who helps the patient with this task, sometimes just clarifying any doubts, other times asking the questions and presenting the possible answers. Clinical trials have many procedures, which may cause the patient to feel lost and abandoned, for this reason it is important that I am always present.
During the visit, the investigator consults the patient and does the registries starting from the text I have prepared previously. In every visit the investigator should ask the patient if he/she has felt any adverse event, if there have been any change in the concomitant medication and if the patient has resorted to other physicians because of any problem. In the end, after all the procedures required by protocol are performed, I make sure everything is registered on the electronic records and we save it. I reinforce the fact that patients should feel comfortable to call me or the investigator when they have any doubt or they feel anything different from normal. If the patient complains about any sign or symptom out of the ordinary it must be reported as an Adverse Event (AE) or a Serious Adverse Event (SAE), depending on the seriousness of the event. The relevant information for reporting an AE is: date of onset and end date, causal relationship with the trial medication, intensity (mild, moderate or severe) and outcome of the event. This information must be reported by introduction of the data on the CRF within 5 days of acknowledgment of the situation. For SAEs, I must report them within 24 hours of acknowledge through paper forms or just by introducing data on the CRF, depending on the protocol, and the required information is more detailed than the necessary for reporting an AE. It is considered a SAE when it meets one of the seriousness criteria (leads to death, is life-threatening, requires hospitalization or prolongation of the same, causes significant, persistent or permanent disability, causes congenital anomalies or requires intervention to prevent permanent impairment or damage). I never had to report an SAE during my internship; on the other hand, AEs are always emerging and I have a lot of experience reporting AEs.
For each patient of a clinical trial, the documents corresponding to each visit are filed in a dossier. Some sponsors/CROs prepare dossiers with separators identified with each visit and the documents necessary for each visit. Other sponsors/CROs do not provide the prepared dossiers, so I have to make my own. Almost every registry is in paper, for example, the EMR created at each visit are printed and filed in the dossier, as well as

exams' reports, other records from other consultations used to build the patient's history, carbonless requisition forms from biologic sample kits, prescription forms, IWRS report's prints, among others.

Just before the visit is finished, we schedule the next visit and instruct the patient for any conditions he/she must comply with in order to be able to do the next visit, for example: if they need to come to the visit fasting; if they must not take the trial drug on the day of the visit; if they have to register any data on diaries provided by the sponsor or by me; if they have to collect any sample for analysis some day before next visit. Anything else they should know before they come to the next scheduled consultation according to protocol, I explain before the patient leaves the hospital. I also ask if patients have expenses' receipts to deliver. Patients participating in clinical trials are reimbursed for any expense incurred by their participation in the trial, so, at every visit I collect these receipts for subsequent refund.

Once the visit is finished and the patient can leave the hospital, I still have some tasks to complete. I take the biological samples to the pathology service to be processed and prepare for shipment of the samples. While the team member from pathology service processes the samples, according to the laboratory manual of the protocol (centrifugation and transfer of serum/plasma for transfer tubes, smears preparation, freezing of tubes that are to be sent frozen, incubation of tubes…), I fill the requisition form with the information required (date of collection, date of birth of the patient, patient number, visit number…). These forms have carbonless sheets, one of which goes with the samples to the central laboratory and the other is filed in the patient dossier. For the shipment, I have to use the so called "air waybills", which are stickers placed on the box that contains the samples, with the information required for the shipment, for example, address of the central laboratory to which the samples are to be sent and account number associated to the sponsor/CRO. If any of the samples is to be sent frozen, I must have requested dry ice the day before in order to be delivered on site on the day of the visit. To book the pick-up of the sample, I must call to the courier and give the following information: client account number, confirmation of who it belongs to, date and period of time for pick-up, country and zip code of the central laboratory, type of samples shipping and its' weight. This way, the pick-up is booked and the courier does the rest. I also schedule the exams needed for the next visit, the scheduling depends on the type of exam and where it is performed. If it is

performed in-hospital, during the initiation visit or before the inclusion of patients, I have to agree with the service (radiology, pulmonology, cardiology or any other) how the exams will be scheduled. If it is performed out-hospital it should be scheduled by e-mail, fax or phone.

Every activity related to the trial medication is performed by the pharmacy, including acknowledge of receipt, accountability, compliance calculation, dispensing and preparation. When compliance calculation and accountability are performed, the pharmacists send me an e-mail after the visit with this information, which I print and include in the patient file.

I must now inform every team member of each patient next visit and the process restarts on the first phase of this process (preparation) for each scheduled visit.

The patient is followed according to the protocol's flowchart, which defines the number of days or weeks between each visit, the visit window (number of days in which the scheduling of the visit may vary) and the procedures. Some protocols require phone contacts to be performed and the flowchart also details which data is to be collected from that contact.

Different protocols have different requirements but I was involved mostly in clinical trials. For trials conducted with inpatient conditions, the required procedures are different and I would need to pay more attention to registries and follow the nurses more closely, because in these types of trials they have a much more active and important role. I did not have the chance to be part of any trial of this nature.

When reaching the end of the trial, participants stop the trial drug at the called "End of Treatment" visit and I have to declare the end of treatment period for that patient on the IWRS. In this phase they enter into the follow-up phase which, depending on the protocol, may be longer (years) or shorter (weeks). In cases where the patient dropout of the study before completing the treatment period, this must also be registered on the IWRS system as an "Early End of Treatment", and the patient continues in the follow-up period of the trial.

Visit procedures: observational studies

Observational studies are much simpler to prepare. Investigators and I are the only involved in the trial. My job is to introduce data in the CRF and I do not have to coordinate with any other team member.

First, I prepare small dossiers, one per patient, with the essential documents of each visit. I include 2 ICFs per patient so that there is a copy to stay with the investigator and another to give the patient. I use a lot of post-it notes to make sure the ICF is properly signed and dated.

The preparation of the visits is based on the information required to introduce on the CRF. I analyze the paper CRF available in the ISF and prepare worksheets where investigators can register the information I need. Since EMR are required, I also prepare the template text that I have mentioned previously and send to them before the visit. I usually prepare the visits all at once, because they are very similar to each other and there are few visits.

I usually am not present at visits from observational studies, because these are very simple visits that doctor can do by themselves. When the visit is complete, I go meet the investigator and bring the documents I have prepared filled with the information from the consultation.

CRF completion

After the end of the visit, it is time to organize the information obtained in that visit and insert the data on the CRF. CRFs may be paper or electronic, I have always worked with electronic CRFs only. On the electronic CRF, each visit has a CRF page assigned and the information obtained in that visit must be introduced in that CRF page. The information required to complete the CRF is the requested information per visit as detailed in the protocol. When the sponsor revises the information I have introduced, sometimes, they issue queries, which represent messages from sponsors' representatives of data analysis requiring explanation of some data. These are resolved by me and, sometimes, I need help from the investigator. I have 5 workdays to introduce the data from a visit on the CRF. The careful and accurate completion of the CRF is a very important task for the sponsor when it comes to the statistical analysis. This is why monitoring visits are performed, to which I will refer later on. It was on the time to complete CRFs that I faced the highest difficulties

with time management, because within visits and all the involved work it is sometimes hard to comply with requirements of CRF filling.

3.2.3 Close-out activities

When every patient from a site has completed the visits defined per protocol, the clinical trial center close-out phase initiates. The sponsor begins the revision of data and issues queries for the data that needs to be clarified and I need to be attentive to the CRF of that trial and solve the queries as soon as possible. When I do not realize the opened queries, the CRA notifies me by sending an e-mail. When everything is completed and free of queries, the PI must sign electronically all the CRF pages. In this phase we are pressured to solve queries and complete CRF pages that were not completed when it was supposed to, this must be done as soon as possible and the sponsor is very persistent about this. At this point the sponsor states different timelines for complete filing of the CRF, queries resolution, database lock, and so on. Sometimes I faced some difficulties with this task, because all the data introduced is revised, which means that clarifications may be required from data introduced in the beginning of the clinical trial/observational study. This is already hard for someone who accompanied the evolution of the patient in the study, but it can be especially difficult if there are queries of old data and the CRC has changed meanwhile. This happened to me close to the end of some clinical trials, when I started the internship. I had to take responsibility for those trials and I faced some constraints, however, with the help of my colleagues and the clinical trials' CRAs, I could overcome this difficulty.

If, in the beginning, the sponsor provided any equipment for the conduct of the trial it is collected in the close-out period. Materials such as unused patient files and unused biological sample kits are not collected. When possible, the materials are reused for other studies.

Close-out visit

The next phase is the close-out visit. In this visit the CRA comes to the site to verify the ISF, the patient files and any other clinical information relevant for the trial. In this visit it is important that the PI is available, because there many documents do sign and date. In the end of this revision, all the documents are filled and ready to be archived.

Unfortunately, I never had the chance to be present in a close-out visit so I cannot describe any activities from this phase of a study.

3.2.4 Continuous activities

Along the conduction of the trials, there are some activities which are not specific from a particular protocol, but have to be performed for all of them.
The main form of contact between me and CRAs is telephone and e-mail. I am not always available for phone contacts because of other activities I may be performing so, I try to compensate and always keep the e-mail updated by answering as soon as possible. A lot of very important information reaches me via e-mail.
As a CRC, I do a lot of telephone contacts, not only with CRAs and other sponsors' representatives, but also with hospital personnel and patients, because I continuously have new issues to discuss with them. Sometimes there is the need to contact patients outside the protocol required contacts. Since I give them my contact they also contact me when they need and the same happens with the investigation team.

Monitoring visits

From time to time, as defined by the sponsor, CRAs come to the site and perform monitoring visits. These visits intend to verify if the clinical trial is being conducted in accordance with regulatory requirements, ICH GCP and the protocol. For this effect, the CRA updates the ISF, revises the patients' files and any other information that is relevant for this activity. Monitoring visits are scheduled in advance and before this visit I must prepare for it by updating the CRF with the data from the performed visits and in accordance with the medical records, and I must make sure the medical records have

registration of every activity performed in the visit. This preparation is made on an on-going basis, as the patients' visits occur, and also before the monitoring visits.
The monitor represents a very important role within the trial, he/she is not only the person who does qualification, initiation, monitoring and close-out visits, a CRA is available to answer any doubts we have at the site and is very helpful when any last minute question about the visits arise.

Patients' expenses

I save the patients' expenses receipts and prepare it for reimbursement. First I must check to which visit each of the receipts correspond to. I have created a document in which I register the amount of the receipt, the corresponding visit, date of visit and date of the receipt, the type of expense (transportation, food or other) and the date the reimbursement was received. This register helps me tracking the expenses that have been already paid and the ones which are still waiting. There are different ways of reimbursing patients: one way is the CRA takes the original receipts and then brings the money to the site; another way is to send the receipts to the financial department of the hospital, the hospital issues an invoice to the sponsor, who pays it to the hospital and the financial department delivers the money to us so we can give it to the patient. Some sponsors make agreements with taxi companies, which is good for the patient, because they do not have to expend money for the travels, and is good for CRCs, because we do not have to control expenses and don't have to manage patients' money.

Preparation of worksheets

Along the trial, especially in the beginning, when the first patients are being recruited, the need of documents for organization of the team emerges. For example, it is very easy for team members who do not contact directly with patients to lose track about which visit is in course and by which patient. In these cases I elaborate worksheets in accordance to the needs of each team member so that the visits' dynamics become more fluid and people don't feel lost.
Also, in order to facility my work in coordinating the team, I elaborate worksheets where they should register the necessary information for the trial required in that moment. A practical example is: when patients go to nurses to collect blood samples, weight and

height measures, vital signs, time of samples collection, among other important information, this needs to be registered and a worksheet works very well in these situations, because nurses know what they need to do as they fill the worksheet. The nurse can, then, do their tasks without my presence, which allows me to do other tasks, such as meet the investigator to sign documents, ask any medical questions about the patient, or any other, while the patient is accompanied by the nurse.

Material stock control

Materials from clinical trials must be continuously controlled, for example, biologic samples kits have expiry dates that must be controlled, otherwise when we need a kit for a visit further on, the kits are all expired and it cannot be used. Also, when the kits are becoming limited, I must order more kits and shipping materials in time for patients' next visits. This is something I must control, because I must not run out of materials otherwise this may culminate in a deviation from the protocol.
Examples of other materials that I should control are: patients' cards, patients' diaries and dossiers to build patient files. For example, for clinical trials for diabetes, I must also control the stock of glucometers, glucose measuring strips and lancets.

Activity map and weekly report

It is very important to keep back-office updated about the activities in the hospital. Weekly, I need to update the activity map, a document where we register patients' visits. It is very important to keep this document updated, because it will allow the back-office to control the activities and the earnings for the company. This also enables to make predictions just so it is possible to plan in advance what we should do to reach set profits. Besides patient's visits, I must also inform about clinical trials/observational studies approvals, otherwise they would not know of the beginning of each study. During the internship, I was not the responsible person to complete the activity map, however, I had the opportunity to update it many times during the internship.
From November 2014, in the end of every week, I started performing a new task: fill a weekly report which should contain the activities I performed during that week and the time spent doing each of those activities. At first, one weekly report was to be completed

by the site and not by each CRC. Ever since the end of January, a new version of the weekly report was implemented and I started completing individual weekly reports.

4. Discussion

After describing the activities developed as a CRC at Blueclinical, I will compare what I have learnt with what I proposed myself to learn, as stated in my learning outcomes. Along this chapter, I will give a personal insight of how this internship changed me as human being and as a professional, which adversities confronted me and what I did to overcome it, what were the aspects that I was more successful at and which aspects I still have to work on in the future.

During this 10 month curricular internship, I was able to learn how to apply the knowledge I have acquired during graduation and the first year of master's degree. In theory, I have learnt about everything that I contacted with during my internship, however, in practice I could not do anything until I was taught how to do it. Without the experience and help of my colleagues during the internship, I could not have learnt so much has I know in little time.

When I was proposed to start a para-curricular internship, I was very apprehensive. I didn't know what the activity consisted on, if I would like it or not, if I would do a good job or if I would like the people I was going to work with. Then I thought, even if something didn't go right, it could only be a good experience, because I was going to contact with the professional world for the first time. I accepted the challenge and started at CHVNG/E, as a CRC, on the 21st of January 2014.

On the 1st of July 2014 the curricular internship took place and, because of superior orders, I went to work at Blueclinical headquarters in Matosinhos. At first, I was not very happy with this change of my functions, because I was leaving the job I was really enjoying to do. Despite my reluctance at first, it was a very nice experience. I had the opportunity to see closely the dynamics of Blueclinical back-office, how my colleagues work and interact, because even though I did the internship for Blueclinical, I was rarely in contact with my colleagues at the back-office. During my activity in the back-office, more important than anything, I have seen the work my colleagues put behind activity maps, financial contracts, medical writing, project management and feasibility tracking. I have learnt the value of their work and I could actually see and feel the importance of these tasks, especially those that are behind our work in the hospitals (activity maps, feasibilities and financial

contracts). In September 2014 I went back to CHVNG/E and, at this time, I was more conscious of the need to help in these activities as soon as possible, so this collaborative network could run well for both sides. While working on the hospital, because there is so much to do, we do not give the necessary attention to what is asked by our colleagues in back-office, and this experience made me see their work in a different perspective. I feel that, besides the added knowledge I have earned from this experience in Blueclinical back-office, I could get to know my colleagues better and develop a healthy and friendly relationship, which was one of my personal objectives. Regarding this new change, it was difficult once again. In Blueclinical back-office there was a very good dynamic between the staff and there was a very good advantage: the tasks I performed during my stay in Matosinhos would only depend on me and on my colleagues, who wanted things to be done as much as I did. In the hospital this is not always a reality, my work depended mostly on other people: investigators, nurses, technicians, CRAs, other professionals and patients, and sometimes some of these people are not very collaborative, which may jeopardize my work. To sum up, the difficulty of this change was that I was leaving a comfort zone that I got to know during the stay in Blueclinical back-office. However, in my perspective, being a CRC is a much more challenging and interesting job, adding the fact that I had already been in CHVNG/E and I already had experience, so the readjustment was very easy. These changes actually made me more determined and conscious of what I wanted. At that point, I had other experiences and I could be more certain that being a CRC was what I wanted and liked to do.

Once I was back to CHVNG/E, I immediately started doing patients' visits. From the moment I have returned, I have started being the principal CRC of some clinical trials and observational studies. For me, this meant I was being trusted and it raised the self-confidence to do my job. Before the beginning of the curricular internship, I had help of other colleagues in every study, which transmitted me safety, because this way I could always resort to my colleagues. When I started assuming the responsibility of being primary CRC, although I could always count on them, I was the person who should follow the development of the trial in the hospital and know the protocol, consequently, I had to do many activities and make decisions on my own. This increase of responsibility raised my self-confidence, which made me be more assertive in my functions. Self-confidence was something that I lacked in the beginning, I was not comfortable talking to doctors,

because I did not know the protocols and didn't understand why I was collecting that signature, for example. Investigators expect us to know everything related with the study and at any moment they would ask me questions I could not answer, which made me very insecure because I did not know every protocol. Since I was not confident about my knowledge at first, I wouldn't answer e-mails unless my colleagues confirmed it was good to send, because we have to be very careful with the kind of language we use, otherwise it may be misinterpreted; and I would also prefer not to answer phone calls, because at any time I could be asked a question I didn't know the answer to, which would make very nervous. These difficulties, with time and experience, no longer represented a problem because, since I started accompanying the new and on-going trials, I knew a lot about every protocol, which helped the improvement of my self-confidence and my communication skills, both written and verbal.

As a CRC, my job is to coordinate the trial staff during all the phases of implementation of a clinical trial/observational study on the site. Investigators are very busy professionals, because they have to do investigation at the same time as they have to meet the requirements they have as clinical practice. As a result, much of my work involves doing what is possible to facilitate their role as investigators, such as adapting to their schedule, which is very limited, and prepare everything I can to save time to the investigator. Sometimes it was hard to adjust my schedule to theirs, because of all the other things I had to do. With time, I became to know at least a day and place where to find each investigator and I made my days more productive, because when I had to get out of the office to solve any issues with investigators I would go on times when I knew I could find as many investigators as possible.

Something that this experience as a CRC taught me was that we can get much more from people with whom we have a good relationship so, develop good relationships was very important, but it represented some difficulties. Investigation teams are composed by many different professionals with different ways of working and different personalities, and I had to adapt to each of them. The fact that I had to interact with so many different people put to test my soft skills. I am a shy person who needs time to develop solid relationships and, because I needed to make contact with people, I had to overcome my limitations. Sometimes, team members from investigation teams are not so nice and refuse to do things they must do as team members. I was a very passive person who did not like to confront or

contradict people, and since team members had to do normal practice and combine it with the activities of clinical investigation, I knew they did not have the time to dedicate to clinical trials/observational studies as it is necessary. Also, I was not always as assertive as I should be and people might think I did not know what I was doing; in addition, they saw me as a very young person, which was not in my favor. With time, I changed some aspects of my personality, because I realized I was not forcing anyone to do something they did not want to do. Investigators compromise with clinical trials/observational studies and the other team members agree to be part of it, so what I was doing was help them complying with something they agreed to do. Once I realized this, I assumed a more assertive position and it allowed me to be taken more seriously and, consequently, strengthen the relationships with many professionals that were part of investigation teams. Self-confidence and assertiveness improved even more with time and experience, and the improvement of these skills helped me in many other situations. Within a team of so many different people, the same posture would not work with everyone, so, I had to adapt my communication and behavior according to the different personalities I had to deal with. All these different personalities and the different circumstances cause conflicts, people get impatient and frequently show willingness to do nothing else for the clinical trial. In these situations, I tried to understand what caused the conflict and what can be done to overcome it. During my internship, most of the conflicts I have confronted myself with were easily solved; however, in some cases resolution is not possible, because the other part is not willing to solve it. For example, when an investigator is not recruiting patients, I must understand why and help in whatever I can help but, in some cases, investigators do not want to be helped in this task and react with some discomfort to this approach. I try to show that my help can only bring advantages, since it will allow the investigator to focus on potential patients to evaluate the criteria, instead of evaluating every patient of their consultation. When, even after this, they do not react well, I do not insist as much. In this case the conflict is not solved and I have to change my approach in order not to increase any conflict. In my opinion, among all the people I had to contact with, the hardest people where the professionals of the investigation teams.

I also had to contact a lot with patients, because I accompanied them throughout all the visits and it was easy to establish a good relationship with all of them. It is important that patients feel they are not abandoned after accepting to be part of a clinical trial and one of

my learning outcomes was to provide patients with the best possible experience they might take from participating in the trial. Patients want to be heard and receive attention, since I was with them along the visits in the hospital, I could give them the attention investigators and other professionals couldn't, and this facilitated the relation. Conflicts also emerge with patients, because visits take too long or because they have to wait too long until its beginning. Some trials have demanding requirements for patients, such as electronic or paper diaries to complete and schedules to meet for medication. Some people do not react well to all of these requirements. I have experienced conflictual situations with patients, however, all the patients I have dealt with were very understanding. To solve these situations the procedure was the same: try to understand what the problem is and do whatever is necessary to facilitate the patient experience in the clinical trial.

In this type of work, I didn't had to interact only with people from the hospital. Regarding CRAs, I am the person who accompany the monitoring visits and resolves most of the pending issues sent by e-mail, phone contact or notified in the monitoring visit. I consider I could achieve a good relationship with all the CRAs I have worked with.

Since there are so many people I have to coordinate and so many other tasks to complete at the same time, sometimes I faced constraints with time management, I found myself looking at the documents in front of me without knowing by which I should begin. To help me with this, I wrote in an agenda every task I had to do in each day, which worked very well. Despite the improvements in this aspect, I still have a lot to improve about my organizational skills, for example, sometimes I faced difficulties in tasks such as answering e-mails and phone calls, which seems so easy to do, because I could not organize efficiently my agenda in order to include those activities.

Assimilation of information was another challenge for me. CHVNG/E had many clinical trials and observational studies, consequently, I had to study many protocols and not only the ones where I was the principal CRC, I also had to be back-up for the other studies, so I needed to know those too. I studied deeply all the protocols, however, they were many and I could not memorize every information of every protocol.

In relation to my professional learning outcomes, I have gained more experience in patients' visits than in other activities. I did not become very experienced in submitting clinical trials and observational studies, because I had a colleague who took responsibility for it. While she was out, I did submission of 2 clinical trials. The activity I gained more

experience regarding submission was preparation of documents and collection of signatures for submission of studies I have been involved. Although critical analysis is very important during every phase of a study implementation, it is very important in this phase. For the few trials I have submitted to the AB, I had the opportunity to understand this. During elaboration of documents and when sponsors send documents to be signed by investigators, it is very important to read carefully each of them, because if there is any error it should be identified right in the beginning, otherwise, it may delay the submission process. For example, if an error is found in the financial contract it should be noticed before submission to the AB, if not, it will be returned for correction, which delays the approval for that contract. I still have a lot to improve regarding this soft skill.

The phase of initiation and development of clinical trials and observational studies, after approval of the financial contract, was the one where I gained more experience. During this phase, I had the opportunity to implement ICH-GCP and to teach investigation team members how to apply it. During the development of a study it must be conducted in accordance with regulatory and ethical requirements, ICH-GCP and the protocol. For this reason, these requirements must be known in order to be applied. Protocols must be studied very carefully, because even though they are very complete, they are not perfect and may present errors or dubious information that need to be clarified, in some cases, this may be translated into an amendment to the protocol. In general, protocols have similar procedures, but it is in the specific ones where the challenge is greater, because I had to adapt to different situations and perform different procedures.

The close-out phase was another one I didn't had that much experience, during my internship I was involved in clinical trials and observational studies which were in the beginning and others that were close to the end, even in these last ones the close-out visit did not occur before I finished the internship. I did, however, experienced the close-out phase, prior to the close out visit, when sponsors start reviewing all the data and request clarification of queries. During my internship, I worked with studies in different phases, however, I did not have the change to follow a study from the beginning until its end. Unfortunately, I never had the opportunity to be present in an audit or inspection, because none of the studies I have participated during my internship were subjected to it in CHVNG/E.

5. Conclusion

My goal during my internship was to learn as much as I could about the CRC job role, so, as a conclusion, I will present the objectives that I have achieved and the ones I have to work on.

Being a CRC was the first professional experience I had in clinical investigation area and it was very fulfilling, because I believe this experience made a CRC with solid knowledge and it changed my personality in a positive way. Even if I work for many years in this area, I would still not know everything and acquire new knowledge, both professional and personal, because there are so many different trials and constantly new different professionals involved in clinical investigation that gaining new knowledge is constant, there is not one day equal to other.

In an overall analysis, I may state that I have been through a lot of constraints but, in general, I have tried to overcome them and I was successful in some achievements. I can never say that I have accomplished any learning outcome completely, because this is an area where complete knowledge is never accomplished, there is always something different to learn.

I believe I made great progress regarding soft skills, and I say this because I can see the change. People respect me a lot more now than they did before and this is the result of a combination of skills that make me a lot more confident.

Regarding CRC experience, I have gained a lot of experience and I am able to adapt to different contexts, which I believe is crucial in this area. However, I did not have the chance to experience all the situations I was expecting in the beginning of my internship. For example, I only had a small experience in a lung cancer clinical trial and I never had the chance to coordinate a clinical trial for acute conditions, which involve hospitalization. Being a CRC does not involve only the coordination activities from patients' visits. There is a long process of feasibilities, submission and close-out procedures that involves it and that require the interaction with different departments from the hospital. I have experience in the development phase of the process, but I did not have the chance to do studies' submissions as a regular part of my work. Regarding close-out procedures, I could not experience it because the chance did not occur.

The fact that I did not had the opportunity to gain more experience in some areas of my work makes me not experienced enough to perform every activity on my own, however, it makes more motivated and willing to change by working hard to keep increasing my knowledge.

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