**Universidade de Aveiro** Secção Autónoma das Ciências da Saúde
**2011**

**MARLENE SOFIA SIMÕES DA COSTA**

# RELATÓRIO DE ESTÁGIO CURRICULAR NO HOSPITAL INFANTE D. PEDRO, E.P.E.

# CURRICULAR TRAINING REPORT IN HOSPITAL INFANTE D. PEDRO, E.P.E.

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Dra. Maria Vale Ferreira da Silva, coordenadora do departamento de investigação do Hospital Infante D. Pedro, E.P.E. e também da Prof.ª Doutora Maria Joana da Costa Gomes da Silva, professora adjunta da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este trabalho à minha mãe.

**o júri**

presidente

Doutora Alexandra Isabel Cardador de Queirós
Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro

Doutor José Carlos Fontes das Neves Lopes
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**palavras-chave**

Investigação clínica, ensaios clínicos, estudos observacionais, coordenador de estudos

**resumo**

O presente trabalho relata as atividades realizadas no âmbito da coordenação de estudos clínicos durante o estágio curricular, inserido no Mestrado em Biomedicina Farmacêutica e desenvolvido no Hospital Infante D. Pedro, E.P.E., em Aveiro, Portugal.

O estágio curricular decorreu no Serviço de Formação e Investigação e teve a duração de dez meses. Durante este período, elaborei três bases de dados que compilam a grande maioria dos ensaios clínicos, estudos observacionais e projetos de investigação clínica submetidos ao Hospital de Aveiro; realizei uma pesquisa bibliográfica e posterior organização da informação sobre a forma de um texto de revisão sobre o tema "qualidade das *guidelines* usadas na prática clínica em oncologia"; e participei em duas reuniões internacionais de investigadores.

Nos primeiros meses de estágio, todo o trabalho realizado por mim era dirigido e supervisionado pela coordenadora do departamento de investigação. Gradualmente foi-me dada a oportunidade de realizar as diferentes tarefas autonomamente. Após alguns meses de treino, eu e a minha colega Diana Soares passámos a assegurar todo o trabalho relacionado com a investigação clínica. Fundamentalmente, o trabalho era focado na coordenação e realização de ensaios clínicos e estudos observacionais. Desta feita, acompanhei vinte ensaios clínicos e quatro estudos observacionais nos serviços de cardiologia, reumatologia, oncologia, endocrinologia e infeciologia.

Durante o estágio curricular tive a oportunidade de realizar variadas tarefas que foram bastante úteis para o meu desenvolvimento enquanto profissional. Desempenhar as funções de uma coordenadora de estudos clínicos permitiu-me aplicar o conhecimento e ferramentas adquiridas durante o Mestrado e, especialmente, permitiu-me realizar as diferentes tarefas de forma cada vez mais autónoma.

**keywords** Clinical research, clinical trials, observational studies, study coordinator

**abstract**

The present work reports the activities of clinical studies coordination during the curricular training, inserted in Pharmaceutical Biomedicine Master's degree, developed in *Hospital Infante D. Pedro, E.P.E.*, in Aveiro, Portugal.

The curricular training took place in Training and Research Service and it lasted for ten months. During this period, I developed three databases that compile the vast majority of clinical trials, observational studies and clinical research projects submitted to the Hospital of Aveiro; I performed a literature search and subsequent organization of the information in the format of a review text related to the theme "quality of oncology clinical practice guidelines"; and I attended two international investigator meetings.

In the first months of the training, all my work was directed and supervised by the coordinator of the research department. Gradually, I was given the opportunity to perform the different tasks autonomously. After some months of training, my colleague Diana Soares and I became responsible for ensuring all work related to clinical research. Mainly, the work was focused on the coordination and conduction of clinical trials and observational studies. Thus, I followed twenty clinical trials and four observational studies in cardiology, rheumatology, oncology, endocrinology and infectious diseases departments.

During the curricular training I had the opportunity to perform a wide range of activities that were very useful to my growth as a professional. Performing the tasks of a clinical study coordinator allowed me to apply all knowledge and tools acquired during the Master's degree and, especially, it was very rewarding as it allowed me to perform the different activities in an increasingly autonomous way.

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# *List of Abbreviations*

| | |
|---|---|
| ABPM | Ambulatory Blood Pressure Measurement |
| AE | Adverse Event |
| AIBILI | Association for Innovation and Biomedical Research on Light and Image |
| CEIC | Ethics Committee for Clinical Research (*Comissão de Ética para a Investigação Clínica*) |
| CNPD | National Committee for Data Protection (*Comissão Nacional da Protecção de Dados*) |
| CRF | Case Report Form |
| CTA | Clinical Trial Application |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | *Curriculum Vitæ* |
| DCF | Data Clarification Form |
| EC | European Commission |
| EORTC | European Organization for Research and Treatment of Cancer |
| EQ-5D | Euro Quality of Life-5 Dimension Questionnaire |
| FMUC | *Faculdade de Medicina da Universidade de Coimbra* |
| GCP | Good Clinical Practice |
| HIP | *Hospital Infante D. Pedro, E.P.E.* |
| HUC | *Hospitais da Universidade de Coimbra, E.P.E.* |
| ICF | Informed Consent Form |
| ICH | The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | Identification |
| INFARMED | National Authority of Health Medicines and Products (*Autoridade Nacional do Medicamento e Produtos de Saúde I.P.*) |
| IP | Investigational Product |
| ISF | Investigator Site File |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| MASCC | Multinational Association of Supportive Care in Cancer |
| PI | Principal Investigator |
| QLQ | Quality of Life Questionnaire |
| RECIST | Response Evaluation Criteria In Solid Tumours |
| SAE | Serious Adverse Event |
| SAM | Medical Support System (*Sistema de Apoio ao Médico*) |

| | |
|---|---|
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| TRS | Training and Research Service |
| UCIC | Coronary Intensive Care Unit (*Unidade de Cuidados Intensivos Coronários*) |

# *Chapter 1: Introduction*

Clinical research plays a key role in the progress of health, since it produces scientific evidence that helps health professionals in their daily clinical practice.[1]

This training report is the compilation of all activities performed during the curricular training, carried out during the Pharmaceutical Biomedicine Master's degree from Aveiro University and it was implemented in partnership with the training and research service (TRS) of *Hospital Infante D. Pedro, E.P.E.* (HIP), in Aveiro, Portugal. The curricular training started in the 6th of September 2010 and ended in the 30th of June 2011, thus lasting for ten months.

In the first four months of the curricular training, all activities were performed under the orientation and guidance of my supervisor in the host institution, Dra. Maria Vale, the coordinator of the research department. After this period, I was allowed by my supervisor to perform the activities in an autonomous way. Starting in the 25th of February 2011, my colleague Diana Soares and I assured the continuation of the work undertaken by the TRS.

During the curricular training period I had the opportunity to accompany all work performed to conduct and coordinate a clinical trial or an observational study, henceforth called *clinical studies*. It was possible to follow the evaluation process of the study site's feasibility to participate in a specific clinical study, as well as the selection visits. It was also possible to observe how a clinical study is submitted to the administration board of HIP, which documents are needed to the submission and all steps done since the request arrives to the hospital and the study receives approval to initiate. After approval, I could follow the development of the studies and all the important steps in their management: study site initiation visits; screening of potential subjects, randomization of subjects, completion of the different study visits and study procedures, handling of study drug (if applicable), notification of adverse events (AE) and serious adverse events (SAE) and so on. In this curricular training, it was also possible to participate in the close out phase of some studies. Additionally, I attended a training course on "Clinical Research Training", participated in two international investigator meetings and created three databases.

This curricular training report is organized in five chapters. First, a description of the state of the art, the characterization of the host institution and the curricular training objectives are presented. Following this, the generic training attended in the host institution/external institutions is presented. Then, the description of the specific training performed in the TRS is exposed. This section includes the description of the followed clinical studies during the period of my curricular training. The fourth chapter presents the discussion of the curricular training and is ensued by the last chapter, with the conclusions.

# 1. State of the art

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published several important guidelines for the conduction of clinical trials. According to the ICH Topic E 6 guideline, a clinical trial (an interventional study) is "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s) (IP), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy".[2] A short description of the principal aims of different types of clinical trials is provided in Table 1.

Table 1. Brief description of the main aims of different types of clinical trials.[3]

| Type | Aims |
|---|---|
| **Treatment Trials** | - Assess the efficacy and safety of a new IP or medical device for a specific therapeutic indication or for a new therapeutic indication;<br>- Assess the efficacy and safety of new doses of an IP already in use;<br>- Compare the efficacy and safety of IP or medical devices;<br>- Evaluate if the new IP or medical device is more effective and safe than the standard medicinal product or medical device. |
| **Prevention trials** | - Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. |
| **Diagnostic trials** | - Find better tests or procedures for diagnosing a particular disease or condition. |
| **Screening trials** | - Test the best way to detect certain diseases or health conditions. |
| **Quality of life trials** | - Explore ways to improve comfort and the quality of life for individuals with a chronic disease (also known as supportive care trials). |

Adapted from "Glossary of clinical trials terms".

Clinical trials are commonly classified into four phases, each one with a specific goal, as presented below:[3]

- Phase I – To find the maximum tolerated dose. To determine the metabolic and pharmacological actions;
- Phase II – Initial effectiveness trial. To evaluate effectiveness, determine the short-term side effects and identify common risks;
    - Phase IIa assess the amount of drug to be given to the subject for optimal results;
    - Phase IIb assess how well the drug works at the prescribed dosage levels;

- Phase III – Efficacy trials. To obtain additional information about the effectiveness and evaluate the overall risk-benefit ratio;
- Phase IV – Post-marketing surveillance for toxicity. To monitor ongoing safety in large populations and identify additional uses.

Nowadays, a phase 0 could be also considered. In this phase, sub-therapeutic doses are used to support the performance of first-in-human tests. These studies are designed to speed up the development of promising medicinal products.[4]

According to Decree-Law no. 46/2004, an observational study (a non-intervention study) is a "study in which medicines are prescribed according to the stipulated conditions in the marketing authorization application; not determined by a study protocol but according to medical practice; the decision to prescribe the medicine is not related to the decision to enrol a participant in the study; [in which] any other complementary diagnostic or evaluation procedure is not performed to participants; and [in which] epidemiological methods are used to analyse the collected data".[5]

There are several professionals involved in the design and conduction of a clinical study. The sponsor is the responsible for the design, implementation, management or financing the clinical study.[5] Then, during the conduction and conduction of the clinical study, in addition to the sponsor, monitors and research team are involved. Monitors are responsible for supervising the clinical study evolution, as well as, for the verification of the data collected.[2] Each clinical study is managed by a research team, which can include medical doctors (known as principal investigator, the PI, and sub-investigators), pharmacists, nurses, laboratory technicians, study coordinators and diagnosis and therapeutic technicians. The research team closely monitors the health of the clinical trial subjects and conduct the study in the study site. A schematic representation of the relationships established between the research team, the monitor and the sponsor is presented below (Figure 1).

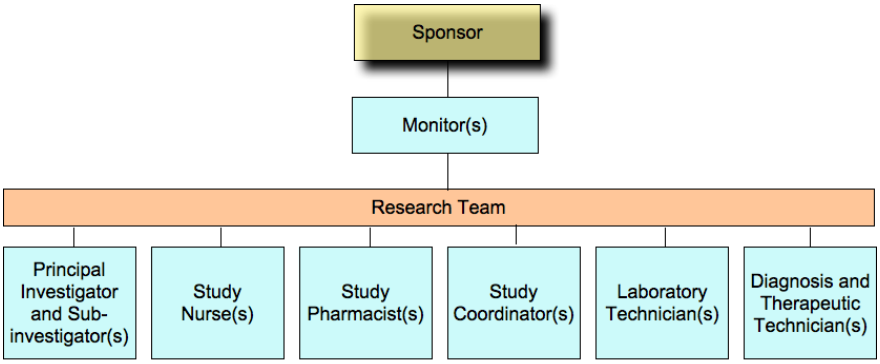
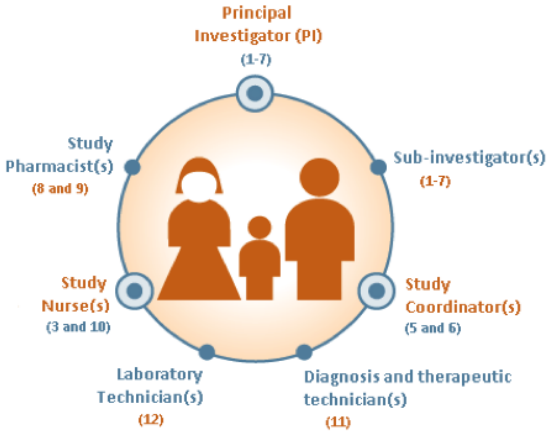



Figure 1. Schematic representation of the relations established between sponsor, monitor and research team.

The research team works together to ensure that all study procedures are met and that the health and well-being of the participants are not compromised. All elements of the research team must sign and date the delegation log. This document determines the responsibilities of each element. The PI is the maximum responsible for the: (1) conduction of the trial at the study site; (2) research team and (3) responsibilities that were delegated on every member of the research team. The PI must ensure that all the elements of the research team are familiarized with the study protocol and with their particular responsibilities. Each element of the research team has different responsibilities in the trial, as is schematized in Figure 2.




1. Inform subject/obtain ICF
2. Determine subject eligibility
3. Perform key trial measurements
4. Medical assessments
5. Make CRF entries and corrections
6. Resolve DCF
7. Review and sign CRF
8. Receipt and storage of IP
9. Dispensation and accountability of IP
10. Take blood/lab samples
11. Obtain/confirm the diagnosis
12. Process blood/lab samples

Figure 2. Schematic representation of the relations established between the different elements of the research team and main responsibilities of each element(s). Abbreviations: ICF – informed consent form; CRF – case report form; DCF – data clarification forms; IP – investigational product.

All elements of the research team should be aware of, and should comply with, good clinical practice (GCP) principles. According to ICH Topic E 6 Guideline for Good Clinical Practice, GCP principles are "a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected".[2] All elements of the research team have to receive qualified training in ICH-GCP principles.

The fundamental document of an ethical clinical research is the informed consent form (ICF). Obtaining informed consent is "a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subjects' decision to participate. Informed Consent is documented by means of a written, signed and dated informed consent form".[2] The ICF has to be obtained before any study procedure is performed.

During the obtainment of the ICF, subjects are given detailed information about the study, including information about the purpose of the study, the tests and other procedures that will be required and the possible benefits and harms of taking part in the study. Subjects who agree to take part in the study are asked to sign and date the ICF and anyone can choose to leave the study at any time. The informed consent process continues throughout the study. In fact, if new benefits, risks or side effects are discovered during the course of the study, the investigators must inform the participants so they can decide whether or not they want to continue to take part in the study. In this situation, participants who want to continue in the study may be asked to sign and date a new version of the ICF. There are some particular situations to be considered when the investigator obtains the ICF: underage subjects, subjects incapable of giving his or her informed consent and illiterate subjects. In case of underage subjects or subjects incapable of giving their consent, the consent should be given by their legal representatives. In case of an illiterate subject, two witnesses (anyone that is not study related) should be called in order to sign and date the ICF.[5]

National and international regulations and policies have been developed to ensure that clinical research is conducted according to strict scientific and ethical principles. In Table 2, the main national and international applicable laws and regulations are presented.

Table 2. Main national and international regulatory framework for clinical research: references and brief description.

| Main regulatory frame | Brief description |
|---|---|
| **European laws and regulations** | |
| Declaration of Helsinki[6] | Ethical Principles for Medical Research Involving Human Subjects. |
| ICH Topic E 6[2] | Guideline for Good Clinical Practice. |
| Directive 2001/20/EC, 4th of March 2001[7] | Related to the approximation of laws, regulations and administrative provisions of Member States relating to the implementation of GCP in the conduct of clinical trials of medicinal products for human use. |
| **National laws and regulations** | |
| Law no.46/2004, 19th August 2004[5] | Approves the conduct of clinical trials of medicinal products for human use. |
| Law no.67/98,26thof October 1998[8] | Law of protection of personal data. |
| Deliberation no. 333/2007[9] | Related to protection of personal data in clinical trials of medicinal products for human use. |
| Decree-Law no. 102/2007, 2nd of April 2007[10] | Establish the principles and guidelines of GCP as regards IP for human use, as well as the requirements for authorizing the manufacture or import of such products. |

## *1.1. Clinical Trials in Portugal – Actual scenario*

The number of clinical trials in Europe is stagnating or even decreasing and Portugal has also followed this trend.[11] According to the data available on INFARMED's (National Authority of Health Medicines and Products) website, the number of submissions of clinical trials is gradually declining, as summarized in Table 3. From the analysis of this table, in 2010, from the 107 clinical trials submitted to INFARMED, 105 were approved. Although, comparing this data with the data from the previous years, it is possible to verify that the number of clinical trials applications is decreasing.[12] This year, 2011, until 6th of May, only 19 clinical trials had been submitted to INFARMED.[12]

Table 3. Clinical trials application submitted to INFARMED – annual statistics: number of clinical trials submitted, authorized, not authorized and average time for authorization.[12]

| Clinical Trial Application (CTA) | 2005 2nd Half | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 1st Half |
|---|---|---|---|---|---|---|---|
| **CTA Submitted** | 108 | 160 | 136 | 146 | 116 | 107 | 19 |
| **CTA Authorized** | 26 | 147 | 131 | 138 | 116 | 105 | 27 |
| **CTA Not Authorized** | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| **Average time for authorization (days)** | - | - | 45 | 43 | 42 | 42 | 45 |

Adapted from INFARMED website.

The decrease of clinical trial applications can be explained by the delay in the approval of new clinical trials by the regulatory authorities and by the administration boards of Portuguese hospitals, which, in some cases, take more than six months. On the other hand, the decrease of CTA could also be explained by the actual economic scenario that Portugal is experiencing, or even by all the bureaucracy involved. Thus, pharmaceutical industries prefer to choose countries where the submission/approval processes are faster.[11]

The TRS facilitates the clinical research work and the existence of this logistic support department may determine that HIP is more often involved in new clinical studies. TRS ensures that, among other procedures, the HIP administration board approval is obtained in an acceptable period.

# 2. Host Institution

HIP is a district hospital with more than thirty years of existence.[13] It serves the population of Aveiro, Águeda, Albergaria-a-Velha, Ílhavo, Oliveira do Bairro, Murtosa, Vagos, Estarreja and Sever do Vouga. HIP works with *Hospital Distrital Visconde de Salréu (Estarreja)* and with *Hospital Distrital de Águeda*. HIP is also connected with *Hospitais da Universidade de Coimbra, E.P.E.* (HUC),[14] the principal referral hospital for HIP.

The mission of HIP is to provide healthcare to its patients, with efficiency and quality, within a framework of sustainable economic and financial development, promoting participation in pre- and post-graduate training, development of clinical research and constant improvement of management techniques.[13] Timely responses to patients' needs and technical and human quality are the goals of HIP in order to be considered a referral hospital and to be recognized as one of the best Portuguese hospitals.[13] The HIP values are: ethic, quality, social responsibility, innovation and respect for the individual.[13]

The hospital of Aveiro was founded in 1895, when the provider of the *Santa Casa da Misericórdia*, Viscount of Silva Melo, became interested in the construction of a new hospital, *Hospital da Misericórdia de Aveiro*.[14] The land was purchased in 1899 and in the 15th of October 1901 the construction of the new hospital began.[14] In 1976, *Hospital da Misericórdia de Aveiro* became *Hospital Distrital de Aveiro*.[14] In December 2002, *Hospital de Aveiro* was included in the group of thirty-one hospitals that have been given the status of Anonymous Society (hospital S.A.).[14] In 2005, it became an Enterprise Public Entity (hospital E.P.E.).[14]

When the first clinical studies began in HIP, the TRS was not established. In this phase, all work was done by the investigators and their research teams. However, the number of proposed clinical studies increased and HIP felt the need to create the TRS. This service was created in the 12th of January 2009 and its main objective is to provide support to the coordination and conduction of clinical studies in order to expedite the clinical research developed in HIP.

The TRS operated under direct supervision of Prof. Doutor Francisco Pimentel, the former president of administration board of HIP. It is composed by two areas: (1) training and medical internship and (2) clinical research.

The clinical research activities in TRS started with Dra. Maria Vale, the first professional who conducted and supervised these activities in HIP. The TRS facilities are equipped with desks, chairs, stationaries, telephones, printer, scanner and computers with access to Internet and Intranet.

TRS is linked to the general logistics support departments, one of the three functional areas of HIP. These functional areas are summarized in Table 4.[13]

Table 4. Organization of functional areas of HIP.[13]

| Functional Area | Departments / Areas |
|---|---|
| **Departments or units of healthcare provision** | Departments (functional units, if applicable) – psychiatry; anaesthesiology (pain unit); pathologic anatomy; cardiology (coronary intensive care unit); surgery; dermatology; stomatology; endocrinology (nutrition unit and diabetic foot unit); gastroenterology; imaging; immunoallergology; immunohaemotherapy; infectious diseases; rehabilitation and physical medicine; work medicine; intensive medicine; internal medicine; nephrology; neurology (stroke unit); gynaecology/obstetrics; ophthalmology; oncology; orthopaedic; otorhinolaryngology; pathology; paediatrics/neonatology; pulmonology; rheumatology; urgency/emergency; urology. |
| **Logistics support departments related to healthcare provision** | Pharmacy; procurement; customer management; sterilization, housekeeping management and social department. |
| **General logistics support departments** | Audits; TRS; information for management; image and communication; legal service; facilities and equipment; environmental management; human resources; financial department and informatics. |

Although TRS was created to give support to all departments of HIP, the main departments that requested support are: cardiology, oncology, endocrinology, rheumatology and infectious diseases departments. A brief characterization of these five departments is presented below.

***Cardiology***

The cardiology department is composed by a coronary intensive care unit (known as UCIC) with five beds, nurse ward with twelve beds, pantry, clinic secretariat and living room. The activity of this department is spread by ambulatory outpatient consultations (hypertension, ischemic heart disease and heart failure), UCIC, emergency and pacemaker implantation. It is possible to perform electrocardiograms, echocardiograms and ABPM (ambulatory blood pressure measurement) in this department. The staff is composed by ten cardiologists, one intern physician, seven technicians of cardiology and twenty-three nurses.

***Oncology***

The oncology department is composed by the nurse ward, clinic secretariat, treatment room and living room. Medical specialists refer their patients to oncologic consultation. When necessary, agreements are established with other institutions to perform some specific exams (*e.g.* biopsies, computerized tomography). Two oncologists, three intern physicians and nine nurses compose the staff of the oncology department.

***Endocrinology***

The endocrinology department is composed by the nurse ward, clinic secretariat, day hospital, pantry and living room. The activity of this department is spread by endocrinology, diabetology, paediatric diabetology, nutrition and high diabetic obstetric risk consultations and day hospital. Two endocrinologists, one intern physician and ten nurses compose the staff of the endocrinology department.

***Rheumatology***

The rheumatology department is composed by the clinic secretariat, living room and consultation rooms. Among others, the activity of this department is spread by rheumatoid arthritis, ankylosing spondylitis, spondylarthritis and lupus erythematous consultations. The staff is composed by three rheumatologists, one intern physician and nine nurses.

***Infectious diseases***

The infectious diseases department is composed by the nursing work rooms, day hospital, clinic secretariat, treatment rooms, pantry and living room. The nurse ward has eighteen beds, of which, six are officially attributed to patients of this department. Two rooms are equipped with negative pressure system and fresh air. The activity of this department is spread by ambulatory outpatient consultations, day hospital and urgency. Samples for specific analytical tests are collected by nurses and are processed either by the HIP or by the HUC. In the last situation, the results are quickly sent by fax or are brought back by the driver who transports the samples, without subject confidentiality prejudice. The staff is composed by three specialists in infectious diseases, two intern physicians and sixteen nurses.

# *3. Curricular Training Objectives*

The main objectives of this training were:

- To learn how to coordinate different clinical trials and observational studies in different medical specialties;
- To apply GCP requirements, protocol specificities and the applicable laws and regulations required in clinical research;
- To develop the personal, interpersonal, search and linguistic skills necessary for working in the clinical research area.

In order to achieve the main objectives, the specific objectives of the curricular training were to:

- Develop databases that gather clinical studies information and that improve their traceability;
- Train on how to properly handle the clinical research concepts;
- Search and organize relevant clinical data;
- Assess the feasibility of clinical studies;
- Verify and facilitate formal clinical studies approval;
- Prepare pre-selection/selection and initiation visits;
- Plan the execution of clinical studies;
- Assist in subject recruitment;
- Prepare study visits and coordinate study procedures;
- Use the interactive voice/web response systems;
- Collect accurate and verifiable data and learn how to properly register that data on case report forms;
- Maintain stocks of study and lab materials;
- Process, store and send study samples to central lab;
- Assure study drug compliance (drug accountability);
- Prepare the documents related to subjects' reimbursements;
- Communicate with sponsor, monitor and with the other elements of the research team and, if applicable with regulatory authorities;
- Prepare monitoring visits and interact with monitors;
- Coordinate study close out visits;
- Safeguard the adherence to GCP, protocol and applicable laws and regulations;
- Archive study documents and maintain study documents updated and organised;
- Prepare study site payments.

# *Chapter 2: Generic Training*

The generic training typically refers to activities held in other departments, whilst the specific training occurred in the TRS. So, this chapter describes all activities performed in other departments of the host institution. However, as my curricular training only took place in the TRS, I will present a brief description of a training course that I attended in an external institution, as well as a summary of a review text that I was suggested to do.

In October of 2010, I had the opportunity to participate in a training course in an external institution. The training course on "Clinical Research Training" was carried out in *Faculdade de Medicina da Universidade de Coimbra* (FMUC), on 29$^{th}$ and 30$^{th}$ of October 2010. This training course was organized by AIBILI (Association for Innovation and Biomedical Research on Light and Image) and it was sponsored by INFARMED and FMUC.

The training was divided into six themes: introduction (clinical research concept and definition and classification of clinical trials and observational studies); ethical principles in clinical research; introduction to biostatistics (design of clinical trials and observational studies); good clinical practices (GCP-ICH guidelines; investigator, monitor and sponsor responsibilities; and the informed consent form); coordination and organization of a clinical trial in a study site; and quality (quality control and quality assurance; audits and inspections).

Attending this training took a total of fifteen hours of duration. This was a very enriching activity because it allowed me to consolidate the concepts and to learn with the lecturers, known experts in clinical research.

Additionally, I had the opportunity to participate in a literature search and subsequent organization of the information, in the format of a review text, related to the theme "quality of oncology clinical practice guidelines". The requested task was to outline a review text to analyse if oncology clinical practice guidelines improve the quality of care received by oncologic patients. To prepare this review text, literature search was performed in MEDLINE and Cochrane Library databases, covering original articles and systematic reviews from 1990 to 2010. Only oncology guidelines were considered. The final version of the review text was send to HIP administration board for the final revision.

Carrying out this task took me about two weeks. To perform it, it was very important to know the purpose of the review. Article selection was a fundamental step for the final review text success. The compilation of all data collected from the different selected articles was the most challenging task.

# *Chapter 3: Specific Training*

## *1. Flowchart: Clinical Trial Steps*

While implementing a clinical trial, there are three key phases related to the regulatory authorities: before, during and after the submission of a clinical trial to regulatory authorities. The flowchart (Figure 3) illustrates the process identifying the inputs, outputs, responsibilities and some important comments. The several steps (1 to 9) are explained below.

Before the submission of a clinical trial to the regulatory authorities, sponsor should make a previous evaluation about some fundamental parameters that could influence the clinical trial success. According to the flowchart (Figure 3), the first step to be performed is the assessment of the study site feasibility to conduct and carry out the clinical study. In this stage, the confidentiality agreement and the feasibility questionnaire are completed (step 1). The confidentiality agreement is established between the sponsor and the investigator/site. This document guarantees the confidentiality of information for a specified period or until the publication of such information.[15] The feasibility questionnaire intends to determine and document the viability of a clinical trial at the study site.[16] This study assesses the available human and material resources, the recruitment potential and if the research team has experience in clinical research and in GCP training.[16-17] According to the feasibility study, the selection of the study sites – selection visit begins (step 1). The Sponsor performs this visit and its main goal is to evaluate and select sites and investigators to conduct the trial.[18] Although the selection visit can be performed by telephone, fax, e-mail or with questionnaires,[18] preferably, this visit should be performed on site. Several topics should be discussed in this visit, such as: study protocol, study drug, regulatory aspects, necessary documentation, research team responsibilities, source documents, monitoring visits, equipment and facilities, recruitment, GCP principles and the possibility of a auditory and/or inspection. Also, human resources, competitive trials on the site, protocol and procedures that may require specific equipment should be discussed, as well as other departments involved (pharmacy, laboratory, etc.).[18]

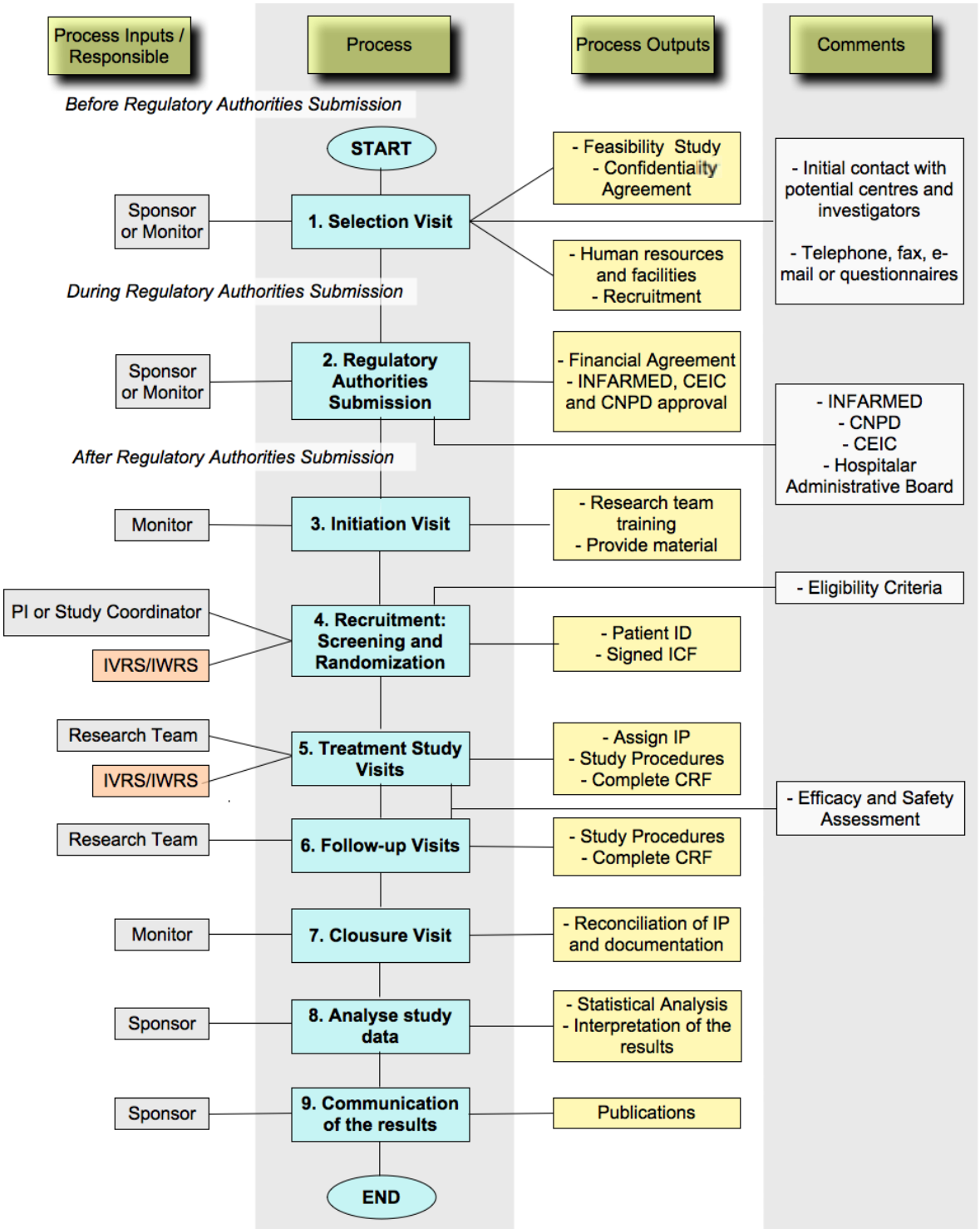



Figure 3. Flowchart representing the main clinical trial steps, before, during and after submission to regulatory authorities. Abbreviations: INFARMED – National Authority of Health Medicines and Products; CNPD – National Committee for Data Protection; CEIC – Ethics Committee for Clinical Research; PI – principal investigator; IVRS/IWRS – interactive voice response system/interactive web response system; ID – identification; ICF – informed consent form; IP – investigational product; CRF – case report form.

The next step is the submission of the clinical trial to regulatory authorities (step 2). Before a clinical trial can be initiated, the regulatory authorities must approve it. In Portugal, these regulatory authorities are: INFARMED (National Authority of Health Medicines and Products); CNPD (National Committee for Data Protection); and CEIC (Ethics Committee for Clinical Research).[5] The study approval by the site administration board is also required and is established by a Financial Agreement. This document is established between sponsor, study site and the PI,[15] and it should describe and acknowledge responsibilities, terms of collaboration, requirements for payment and reimbursement, publication and intellectual property terms, indemnification and insurance, subject injury coverage, grounds for termination of contract and possibility of amending contract terms in the future.[15] Direct and indirect costs are also documented in the financial agreement.[15] Direct costs are the costs related to research team payments and the indirect costs are the costs spent with the use of complementary means of diagnosis and therapeutics, unintended hospitalizations and expenses and losses incurred by participants.[5] Usually, the sponsor delegates these first presented steps on the monitors.

After the approval by the regulatory authorities, the trial can now start. This process begins with the initiation visit (step 3). The main goal of this visit is to leave the site totally able to initialize the trial.[18] In this visit, the monitor explains the research team's responsibilities, study procedures, case report form (CRF), AE and SAE notification, study drug, clinical reports and source documents, ICF and biological samples collection.[18] At the end of this visit, some important tasks should be fulfilled: delegate responsibilities and training the research team, provide all necessary material, explain all study procedures and obtain important documents like the *curriculum vitæ* (CV) of the different team members.[18] All study documentation is archived on the Investigator Site File (ISF).[18]

Investigators can now recruit participants to the trial. The recruitment period is a period during which the investigator is attempting to identify and enrol participants who meet the eligibility criteria.[3] The selected subjects must perform the screening visit and have to sign and date the ICF, before any trial procedure is performed. The identified potential participants are screened in order to ensure that they meet all eligibility criteria and, consequently, they can be randomized to the trial (if applicable) (step 4). The eligibility criteria are summary criteria that determine if a person may or may not be selected to participate in a clinical study.[3] These comprise the inclusion and the exclusion criteria.[3] Randomization is a method by which participants are randomly assigned to a treatment arm (for randomized clinical trials).[3] Randomization is made using the interactive voice response system or interactive web response system (IVRS or IWRS). Preferably, the investigator should perform this task; however the study coordinator can assume this responsibility, always under the investigator supervision. During the randomization call, an assignment of a subject identification number will be issued and the subject will be assigned to a study treatment arm. Usually, this is the first time that patients are assigned to the study drug. Specific study drug kit numbers, assigned by the IWRS or IVRS, identifies the study drug assigned to a specific subject. In non-randomized

clinical trials, the study drug is dispensed to subjects without using the IVRS/IWRS. A clinical trial in which the investigator and the subject know which treatment is being administered to the subject is called an "open-label study".[3] If one or more parties involved in the clinical trial are unaware of the treatment assignments, the trial is called "blinded". A study in which one part, either the investigator or the subject, is unaware of the treatment assignments is called a "single-blind study".[3] A clinical trial in which both investigator and subject are unaware of the treatment assignments is called a "double-blind study".[3] There are also clinical trials where the investigator, the subject and the data analyst are unaware of the treatment assignments. In this situation, these clinical trials are called "triple-blind studies".[19]

There are some clinical trials in which a run-in period is established. This period is established in some protocols for several reasons, depending on the purpose of the trial itself (*e.g.* adherence to study drug, confirmation of eligibility criteria). Then, the clinical phase of the trial begins – the treatment study visits (step 5). Treatment study visits are performed according to periods established in the study protocol and vary from protocol to protocol. A series of clinical tests and procedures will be performed at specified intervals throughout the study.[18] For each visit, there are study procedures that must be strictly performed. Some study procedures examples are: obtain the ICF; demographics and medical/surgical history (*e.g.* age, birth date, race, documentation of any clinically significant medical condition, tobacco and alcohol use); physical examination (*e.g.* weight, height); vital signs (*e.g.* blood pressure, heart rate, body temperature); perform exams (*e.g.* electrocardiogram, echocardiogram, computed tomography, X-ray); clinical laboratory tests (*e.g.* chemistry, coagulation, haematology, urinalysis); pregnancy test; concomitant medication; AE and/or SAE; quality of life assessments; dispensation of study drug.[18]

After the investigator and his research team meet all study procedures for a particular visit, they can, through IVRS or IWRS, assign the subsequent study drug kit numbers to a subject. Generally, clinical studies require the dispensed study drug kit numbers to be confirmed in the IVRS or IWRS to guarantee that the right kits are dispensed to the right subject. For each visit, the study pharmacist should verify the returned study drug, which is designated as "drug accountability". This task consists in verifying the number of returned pills, comparing it to the total number of dispensed pills (in case of oral pills). Based on dispensed/returned study drug, study pharmacists perform study drug accountability and adherence calculation. If non-adherence is detected, they should communicate with the investigator. All study drugs at the study site should be adequately stored and the temperature and moisture has to be monitored at the pharmacy.[20]

At the end of the treatment clinical phase or in case of early discontinuation of a subject, the end of treatment visits and subsequent follow-up visits are performed (step 6). In the end of a treatment visit, patients stop taking the study drug and depending on the therapeutic area, they may be switched to a commercial medication or continuing taking the study drug (outside the context of the trial) until it is available on the market, in case there are no alternative therapeutics available and the patient is clearly

benefiting from the study drug.[5] Depending on the trials, at this visit, some procedures may also be performed in order to assess patient progression during the trial like cognitive tests and health and life questionnaires. All patients are followed after the last dose of study drug is administered. The purpose of these follow-up visits is to assess the subjects' clinical status after study drug discontinuation. At the end of the clinical treatment phase or in case of early discontinuation of a subject, an end of treatment visit is also performed.

All visits must be introduced in the CRF. These forms are used to transmit the information collected during the study to the sponsor and to the regulatory authorities, if applicable.[18] The investigator records all required data in the subject files and these subject files serve as source documents (original documents, data, and records[2]) for the trial. Source documents have to be available at monitoring visits and also in case of audits and/or inspections. The investigator is required to prepare and maintain adequate case histories designated to record all observations and other data pertinent to the trial. All data reported in the CRF must be derived from source documents and must be consistent with the source documents.[18] In the monitoring visits, the monitor confirms all the information entered in the CRF with the source documents: if the patient had all the inclusion and none of the exclusion criteria; if all the procedures were performed for each visit; all the concomitant medications and AE recorded; the study drug dispensed to the patient was the one assigned by the IVRS/IWRS; etc. The investigator should ensure that the data is timely reported, being both complete and accurate.[16]

The close out of the study (step 7), also known as closure visit, is performed when: (1) the study site meets the study protocol; (2) the sponsor decides to finish the trial; or (3) by the request of investigator, CEIC/Local Ethical Committee or other regulatory authority. Among other tasks, in this visit, the monitor should: verify all open issues that are present in the last monitoring report; verify the list of equipment to be returned from site; ensure the final reconciliation of study drug; ensure the final reconciliation of all documentation; confirm that all CRF are complete and with no open queries. The investigator is also reminded about the need to archive all study related documentation during a minimum period defined by the sponsor.[16]

When a clinical trial ends, this conclusion should be notified to INFARMED, CEIC, CNPD and to the administration board of the site within ninety days.[5] However, if the end of the trial is anticipated, the notification to regulatory authorities must be made within fifteen days.[5] Trial data are then analysed by the sponsor and the results must be published (steps 8 and 9).

The three key phases related to study submission in clinical trials are also applicable to observational studies. In order to perform these studies, the Local Ethical Committee's (ethical committees from study sites) positive opinion is required, along with a positive opinion from the CNPD. When the CNPD and the Local Ethical Committee approve the study, the submission documentation is conducted to the study site administration board to obtain approval for the conduction of the study in their facilities. The establishment of a Financial Agreement between sponsor, study site and PI determines this approval.

After the approval by regulatory authorities, the study can be initialized and the investigator can now recruit participants to the study. The subjects selected to perform the screening visit must also sign and date the ICF, just like in a clinical trial.[5] There are also clinical studies that do not require the obtainment of the ICF (*e.g.* retrospective studies). At the end of the study, data is also analysed and the results are communicated.

# 2. Work performed as Clinical Study Coordinator

According to the Association of Clinical Research Professionals, a Clinical Research Coordinator or Clinical Study Coordinator "works at a clinical research site under the immediate direction of a PI, whose research activities are conducted under GCP and ICH guidelines".[21] According to the same association, a clinical research site is "the location(s) where trial-related activities are actually conducted".[2]

Since my curricular training involved the collaboration and contact with health professionals from some medical departments from HIP, my supervisor introduced me in the different departments as a trainee.

The next two topics present the activities performed during my curricular training: databases creation (2.1.) and followed clinical trials and observational studies (2.2.).

## 2.1. Databases Creation

At the beginning of my curricular training, one of the first activities that I performed was the creation of three databases: one for clinical trials, other for observational studies and the last one for clinical research projects. These databases were created to organize a repository of clinical studies information with the aim of optimizing the studies archive, as well as making the study search faster.

The databases for clinical trials and observational studies presented information like: study title, study phase (in case of an interventional study), sponsor, approval date in HIP, start date of the study in HIP, PI, sub-investigators, study pharmacists and nurses, the actual state of the study and the department(s) where the clinical study is performed. All studies/trials were entered in the respective database and they were associated with a study code, in the format XX–XXXX–X (this code corresponds to department code – year – study acronym). When a new clinical study was approved in HIP or when a clinical study was finished, databases were updated.

The database for clinical research projects presented information like project title, investigator, supervisor, co supervisor, approval date in HIP and the department(s) where the research project is performed. Like the clinical trials/observation studies databases, all clinical research projects were also associated with a code, in the format XX–XX–XXXX (this code corresponds to department code – study number – year). When a new project was approved in HIP, this database was updated and the submission documents were properly labelled and archived in the appropriate folders.

Carrying out this task took me about three to four weeks. This first activity was a very important task and very well positioned in time because it allowed me to be aware of the number of clinical studies that

existed in HIP, helped me to know the investigators and research teams involved in clinical research, as well as to learn about the different therapeutic areas studied, study phases and main purposes.

## *2.2. Followed Clinical Trials and Observational Studies*

In HIP, there were several ongoing clinical trials and observational studies that required additional effort and availability from the research team. There were many medical departments that conducted clinical trials and/or observational studies. However, just some of them ordered for the involvement of TRS. The main clinical departments where I have performed as a clinical study coordinator were, as previously stated: cardiology, oncology, infectious diseases, endocrinology and rheumatology. In these five departments, I had the opportunity to follow twenty clinical trials and four observational studies, distributed as listed below:

- Cardiology – Seven clinical trials;
- Oncology – Seven clinical trials and four observational studies;
- Infectious diseases – Two clinical trials;
- Endocrinology – One clinical trial;
- Rheumatology – Three clinical trials.

First, I will provide a description of all tasks performed as a clinical study coordinator, which are identical for all studies and, finally, I will present a more detailed description of the activities performed in each particular study (if applicable).

Performing clinical studies coordination in HIP occurred during all curricular training, in a period of ten months. The main activity performed as clinical study coordinator was the coordination and organization of the approval process and conduction of clinical trials and observational studies. Some important procedures done for all clinical studies were to:

- Assess clinical study feasibility;
- Verify and facilitate formal clinical study approval;
- Prepare pre-selection/selection and initiation visits;
- Plan the execution of clinical study;
- Assist in subject recruitment;
- Prepare study visits and coordinate study procedures;
- Access to IVRS or IWRS;
- Collect accurate and verifiable data and register all required data in CRF;

- Maintain stocks of study and lab materials;
- Process, store and send study samples to central lab;
- Assure study drug compliance (drug accountability);
- Prepare the documents related to subjects' reimbursements;
- Communicate with sponsor, monitor and with the other elements of the research team and, if applicable with regulatory authorities;
- Prepare monitoring visits and interact with monitors;
- Coordinate study close out visits;
- Safeguard the adherence to GCP principles, protocol and applicable laws and regulations;
- Archive study documents and maintain study documents updated and organised;
- Prepare study site payments.

All these activities are described below, showing the tasks that I performed during my curricular training.

***Assessment of clinical studies feasibility***

When sponsors are recruiting study sites to participate in their clinical studies, they send out interest feasibility questionnaires to potential sites. Usually, this first contact with the study sites is done with potential investigators, but it can also be performed with study coordinators, if they exist at the study sites. When a study site receives a feasibility questionnaire, it is usually accompanied by a brief protocol synopsis.

During the curricular training period, I had the opportunity to verify, at least, sixteen study feasibility assessments. Although the questionnaires were related to different studies from different sponsors, I noticed that the required information was very similar: logistical conditions, human resources/staff availability, subject recruitment, research team experience and training. My specific functions in this feasibility evaluation process were to: obtain the confidential agreement; ensure completion of all required fields/questions; and establish a good communication with the investigator(s) and with the monitor in order to complete; and to return the feasibility questionnaire in two to three days.

***Verification and facilitation of formal clinical study approval***

When a new study was submitted to HIP, before sending the submission documents to the administration board, I reviewed the submission file in order to verify if the necessary documents were present and to evaluate if the financial agreement was established according to the HIP rules. A checklist of all of the required documents was filled out. According to the HIP internal requisites, the submission file must include: study protocol; solicitation letter; ICF copy; investigator CV; authorization of the head of the department where the clinical study will be performed; positive opinion of the CEIC (in case of an interventional study) or of the Local Ethical Committee (in case of an observational study); positive opinion of CNPD; positive opinion of the INFARMED (in case of an interventional study); positive opinion of the HIP

administration board; financial agreement signed and dated by the sponsor and the PI; and insurance certificate (in case of an interventional study). If all documents were present, I would send the submission file to the administration board for the final approval. The establishment of the financial agreement determines this approval (three originals of the financial agreement were signed and dated by the sponsor, the PI and by the administration board of HIP). After this process was completed, I would send two originals of the financial agreement to the monitor.

In the submission process, my specific functions were to: review the submission file; propose amendments, corrections and/or improvements to the submission documents; establish a good communication with all involved parties in order to obtain the signed and dated financial agreements; produce and send the approval craft to the monitor; and send two originals of the financial agreement to the monitor in no more than two to three weeks. During the curricular training period, I had the opportunity to work with, at least, twelve submissions to the administration board of HIP.

***Preparation of pre-selection/selection and initiation visits***

The usual procedure for pre-selection/selection visits implies that the monitor comes to the study site to perform this visit. When the pre-selection/selection visit was not an in-person visit, my roles were to: collect the necessary documents used in the submission process (e.g. investigators' CV) and send them to the monitor; facilitate the communication between the PI and the monitor; and clarify the monitor's questions. Additionally, I had to ensure that the research team reserved the planned date for the initiation visit. I only had the opportunity to witness one selection visit.

Initiation visits were always performed in-person. In these visits, I received adequate training on the protocol along with the research team (*e.g.* study objectives, ICF, AE/SAE reporting, GCP principles, study drug, CRF); some important documents were collected (*e.g.* subject pre-screening logs, delegation log); and the recruitment was discussed. In most cases, some documents were still missing, so I had to collect them and send them to the monitor (*e.g.* research team's CV, delegation log, financial disclosure forms). During the curricular training period, I had the opportunity to follow, at least, ten initiation visits.

***Planning of clinical study execution***

The study planning should start when the sponsor approves the participation of HIP in the study. At this point, the PI, the research team and I talked about issues related to the next steps of the clinical study, including the assessment of the realistic way to include patients. Additionally, if the study visit scripts to the different visits, study drug dispensation forms, nurse forms, and visit planners were not provided by the sponsor and if the sponsor allowed me to do/use them, I prepared and adjusted them.

Whenever a new clinical study started, planning its execution was fundamental. From there, at least once a week, it was necessary to review the performed work in order to check if all planned goals were achieved.

The teamwork and the cooperation with all health professionals involved in the different studies are essential to correctly plan the work.

***Assistance in subject recruitment***

Whenever a new clinical study started in HIP, the PI, the sub-investigators and I, tried to select possible subjects to screen with the objective of enrolling them in the study. After defining a subject pre-screening list, we carefully assessed the eligibility criteria in order to certify that the selected potential participants met all the inclusion criteria and none of the exclusion criteria. This was a fundamental task to ensure that the research team reached the number of proposed subjects – recruitment objective (the proposed goal agreed in the financial agreement to our study site). To select potential participants in retrospective studies, I needed to carefully analyse Medical Support System (SAM) application and/or clinical patient files from patients who were medicated with the therapeutic indication in study. In this process, I had also to check if all eligibility criteria were met. In this phase, before enrolling or randomizing a new subject, the eligibility criteria were also verified or, if applicable, re-verified.

In cooperation with the PI and/or investigators, during the recruitment process, my functions were to: identify and select potential subjects; define a subject pre-screening list and, later, a subject enrolment list; analyse the eligibility criteria; and enrol and/or randomize subjects to the study.

Compliance with all eligibility criteria is essential and it should be respected by all investigators. These criteria are established based on safety parameters that should be considered when including subjects to ensure their safety and well-being.[3]

***Preparation of study visits and coordination of study procedures***

After the enrolment of a subject, I had to schedule the next study visits according to study protocol. My main function was to ensure that all required study procedures for each visit were completed. Thus, the preparation prior to the study visits was essential. To prepare a study visit, I resorted to study protocol. Additionally, I prepared all necessary forms (considered source documents) to register all clinical data, such as: study drug dispensation form, nurse form, study visit script, health questionnaires required by protocol (*e.g.* EQ-5D, Euro Quality of Life-5 Dimension Questionnaire, a standardized instrument for use as a measure of health outcome) and other specific forms required (*e.g.* physical examination forms). In certain visits, it was also necessary to prepare study kit(s) for samples collection: blood and/or urine. Kits were provided by the sponsor/central lab and were already prepared for a particular visit. However, I had to identify the collection tubes, slides or other collection materials with the subject details.

One important visit that should be carefully prepared is the randomization visit. This visit, when subjects are assigned to a study treatment arm, coincided mainly with the first study visit. However, some study protocols defined a run-in period. In these situations, the randomization visit was performed after the run-

in period completion. To randomize a subject, I had to access to IVRS or IWRS and introduce some required subject details. The IVRS/IWRS allocated the subject to a study treatment arm and also gave the subject identification number (also known as subject ID/subject number). Usually, the assignment of study drug happens only after subject randomization.

When preparing a study visit, I ensured that the subjects would attend those appointments. Thus, some days before the study visit, I contacted the subjects to remind them of the scheduled visits. Contacts were also made to schedule some complementary exams.

Three to four study visits per week were appointed and carried out. All visits were prepared in advance to ensure that all protocol required procedures and measurements were met.

To maintain the research team informed about the study visit appointments, "Study Visit Planners" were prepared and placed in the physicians' workroom. These visit planners were updated monthly.

***Accessing to IVRS or IWRS***

To expedite some clinical research activities, two systems are used: IVRS and IWRS. The IVRS is a phone system application that prompts callers with recorded messages, menus and options and processes voice input and/or touch-phone keypad selections from these menus. The IVRS script responds to this input by providing appropriate information in the form of voice answer.[22] The IWRS is the web-based equivalent of IVRS, where instead of the telephone, a secure webpage is used as the interface with a central computer, enabling the user to select menu options and to enter and receive data and instructions.[23] Often, these systems are combined with fax/e-mail service and perhaps with other media. This allows users to receive evidence of the performed activities. These two systems are highly accepted by users as they provide results in real time. They are used to randomize subjects, screen subjects, assign study drug, withdraw subjects, confirm attributed study drug kit numbers, suspend or restart study drug, among others.

All platforms of IVRS/IWRS require a login at every access, from which I can normally make the transactions. At the beginning of a new clinical trial, I received training on how to properly access and use the study IVRS/IWRS by the sponsor, who also provided me with the first access codes. For the platform of each study, I had a different username and password.

I accessed the IVRS or IWRS platforms to: randomize subjects to a study; obtain the subject identification number; assign the subsequent study drug kit numbers; discontinue/interrupt/re-start study drug; confirm study visit numbers and/or study drug kit numbers; and to perform the unblinding procedure. Some systems were prepared with more option menus, specific for the different studies.

In rare cases, the unblinding of the study drug is required. This may occur as a result of an adverse event where it is necessary to know the study treatment arm that was being administered to the subject in order

to determine how to treat the event. I had the opportunity to perform one unblinding (or code break) procedure. Unblinding is the process by which the randomization code is broken so that the investigator and the research team become aware of the treatment assignment for a specific subject participating in a clinical trial.[2] In most cases, the person permitted to perform the unblinding procedure is restricted to the PI. However, I was consented by the PI to perform this task. Thus, it was necessary to activate the code break envelope provided by sponsor. These new access codes allow access to a new menu option in the IVRS/IWRS: unblinding. By accessing this new menu option, it was only necessary to provide patient details and the system immediately returned the treatment that the subject was receiving.

During the curricular training period, I had the opportunity to work with seven different IWRS platforms and with three different IVRS platforms.

***Collection of accurate and verifiable data and registration of all required data in CRF***

According to ICH E 6 Guideline for Good Clinical Practice, a CRF is "a printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject".[2] A CRF is a data collection tool used to support investigators and coordinators in capturing all protocol-required information. The sponsor designs the contents of the forms and distributes them in paper or in electronic format to all study sites where the clinical study is being conducted.[24] CRF should be built so that they: gather accurate information that answers study questions and are consistent with study protocol; organize and label forms and fields so that data entry is intuitive; and avoid duplication of data.[25]

The research team must ensure that data is entered accurately and its verification is possible at any time of the study. The CRF should be completed by authorized people, clearly and accurately. It must not be strikethrough and all forms and fields have to be completed. Any change or correction in the CRF (in case of paper formats) should be dated and validated by signature and should not hide the original data.

For all electronic CRF, I had a different username and password. Each time I accessed these systems I was prompted to enter my login information. From there, I could make the transactions. At the beginning of a new clinical study, I received training on how to properly access and use the study CRF.

All required data was entered in the CRF in no more than five working days after each study visit. When some data was missing, I scheduled an appointment with the investigator that performed the incomplete visits in order to get this information.

During the data entry process, some automatic queries can be generated. Queries are related with questionable information. This means that the entered information is not valid or complete or that some data is missing. The data managers and monitors can also generate queries. These queries are used to request more information or to clarify the information provided. Each query must be resolved by the investigator or by the study coordinator. Then, queries are re-assessed by the sponsor. If the query is still

not clarified, a new query is generated and it will only be solved when the data manager/monitor is clarified. I tried to clean all queries in two to three days. A prompt response by the research site can be used to evaluate its performance.

I had the opportunity to work with both formats of CRF: six different electronic platforms and two CRF in paper format.

***Maintenance of stocks of study and lab materials***

All clinical trials or observational studies had specific study materials. These materials were composed by:

- Laboratory materials – kits for collection of samples, lab requisition forms and carton shipment boxes for sending samples at room temperature or in dry ice, specimens transport bags, absorbent tube shuttles and waybills.
- Study materials – study visit scripts, study forms, study drug dispensing forms, some specific questionnaires, SAE forms and other specific documentation/forms.

To avoid missing study material, I filled a reorder form to reorder supplies to HIP. This reorder form was faxed to a dedicated fax provided by the sponsor/central lab. The management of stocks is very important to ensure that, throughout the study, all necessary materials are accessible in the study site.

***Processing, storage and sending study samples to the central lab***

During my curricular training, I had the opportunity to handle three different types of study samples (or specimens): blood, urine and histological samples (tumour cells). Sample collection for research protocols requires specific attention to the proper timing, collection, labelling, processing, storage, and shipping.

The first step to be performed was the preparation of study kits. Normally, clinical laboratory kits were used to collect study samples. Each kit was manufactured for a specific visit and was labelled with sponsor name, protocol number, study visit, and expiration date. When preparing lab kits, it was necessary to label all collection tubes. To properly label the tubes I should: fill out the required information on the requisition label; label the tubes at the time of sample collection and confirm that subject identification and other required information was correct; place the label in a vertical position and never wrap the label around the tube horizontally; do not adhere the label on the cap of the tube and do not cover any written information with the label. Some sponsors provided study kits already labelled. In this situation I just needed to properly fill out the required information.

The second step of this process was the preparation of study samples. After collection of samples, according to the study lab manual, it was necessary to prepare them for dispatch:

- Blood samples – After collection of blood samples I should: completely and gently invert tubes; allow the blood to clot; centrifuge tubes using a defined amount of revolutions per minute and during few minutes; identify the transfer tube with the appropriate labels; transfer plasma, using a disposable pipette; avoid transferring any red blood cells; re-centrifuge if necessary; discard the collection tubes after transferring the plasma; secure caps; and store and send to central lab. Some collection tubes were sent without centrifuge. In these situations, I just needed to completely and gently invert tubes and store and send to central lab. These procedures can vary depending on protocol requirements.
- Urine samples – When required per protocol, in certain study visits, subjects were provided with a urine vial. To properly collect urine sample subjects must be instructed that they must discard the first morning urine. Also using a pipette, a portion of urine was transferred to the transfer tube. These transfer tubes were also properly labelled. These procedures can also vary depending on protocol requirements.
- Histological samples – In this situation, sample preparation was made by a clinicopathological technician. Concerning this type of samples, I just had to send them to central lab in order to be analysed.

When handling and preparing samples, appropriate safety measurements should be taken, including the use of adequate protective equipment.

The final step was the preparation of samples to send to the central lab. Samples were shipped at room temperature or they were stored in an upright position at -20$^{o}$C on site and shipped later on dry ice (frozen shipment). A lab requisition form accompanied all study samples. The minimal required information that should be included in the lab requisition is:

- Accession number or requisition number (this number associates the requisition to their respective labels);
- Subject identification number and birth date;
- Collection details;
- Applicable study visit.

Some lab requisitions presented the instructions on how to process lab samples. If it was not presented in the lab requisition, these instructions were presented in lab manual provided by the sponsor/central lab. When samples were prepared and all requisition form fields were carefully filled, I had to prepare the shipment. A shipment involves two steps: preparing the shipment box and arranging a pick up. To prepare the shipment box, I had to place the labelled tubes into the absorbent tube shuttles and place it inside the

specimen transport bag. If samples were shipped at room temperature, I placed the specimen transport bag in the carton shipment box with the respective requisition form. If samples were shipped in dry ice, the procedure is the same but I had to use a carton shipment box lined with foam. Then, I had to fill the box with dry ice. Dry ice must be manipulated with special gloves and it should not be stored in a confined space. Dry ice handling has to be made according to International Air Transport Association rules. For all frozen shipments, I had to order dry ice by sending a specific form to the central lab. Finally, I had to arrange a pick up. To complete this task, I had to call to a carrier customer service and schedule a pick up day and time. Each individual shipment was combined under a single waybill. It helped to ensure timely, accurate and secure delivery. At least, a waybill should include:

- Payer account name;
- Person contact name;
- Sender reference number, name and address;
- Receiver name and address;
- Shipment details;
- Full description of contents.

A carrier collected our samples and took them to the central lab. Lab results are later available by fax or e-mail.

***Assuring study drug compliance (drug accountability)***

Study site should document study drug receipt, study drug dispensing and return of study drug (used and unused study drug kits). This is a study pharmacist function. However, I also performed such records to ensure that everything was adequately documented (ensure the adequate flow of study drug in and study drug out).

When the study drug is received at the study site, it is important to inspect the shipment in its entirety and the proper study drug receipt records should be filled. Study drug should always be stored in a secure location and its storage conditions should be closely monitored. Temperature logs should be maintained in the storage area to ensure that the product remains viable. When dispensing study drug to a subject, I filled out the study drug dispensation form, recording the date, subject number, study drug kit numbers assigned/dispensed and the amount dispensed. When a subject returned the study drug, the amount of used and unused study drug were also documented, as well as any study interruption, inadvertent loss or destruction.

Counting the used and unused study drug was a very important task in order to evaluate the subject study drug compliance; this is, to know immediately if subjects were properly taking the study drug. Drug

compliance is usually assessed in percentage and, whenever bad study drug compliance is detected, the PI and monitor should be informed.

***Preparation of the documents related to subject payments***

According to Law nº 46/2004, subjects included in a clinical trial are not granted with any incentives or financial inducements, but the reimbursement of the expenses and the compensation of damages incurred from the participation in the study are allowed.[5]

The expenses that were accepted by sponsors were: travel costs to and from study site; meal expenses incurred during the days of study visits, if the presence was required; and compensation for hours/days lost from work to attend the study appointments. All expenses must be accompanied with the respective invoice. Compensation for hours/days lost of work was only refunded if the subject presented a declaration of the employer that demonstrates the labour absence of subject during the study visit periods. All invoices were collected, verified and identified with subject number; then, they were forwarded to sponsor. Some specific documents were also filled to accompany the invoices in order to identify the subject and to explain/characterize the invoices.

In our study site, we had the need to arrange a taxi service to make the transportation of some patients. In these situations, I had to collect the taxi invoices, send them to sponsor and, later, perform the payments. Two clinical trials required me to arrange a taxi service.

***Notification of adverse events and serious adverse events***

According to guideline ICH Topic E 6, an AE is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment".[2] AE can be symptoms (*e.g.* nausea, chest pain), signs (*e.g.* tachycardia, enlarged liver) or an abnormal result of an intervention (*e.g.* laboratory finding, electrocardiogram finding). An AE can also be an undesirable medical condition occurring at any time, including the run-in period, even if no IP had been administrated.[2]

Prior to enrolment, the PI and I recorded each subject's medical condition(s) – subject medical history. During the study, the PI and I continued alert to any changes in the clinical condition(s) and the occurrence of AE. The AE were collected from the time that ICF was signed, throughout the treatment period and until study completion (including follow-up period, when it is required per protocol). All AE were reported in patient files and in the CRF.

SAE collection also began after the subject had signed the ICF and it should be reported to sponsor within twenty-four hours, starting at the time that the research team is aware of the SAE. Also according to guideline ICH Topic E 6, a SAE is any clinical event that fulfils at least one of the following criteria: is fatal (results in death); requires initial or prolonged inpatient hospitalization; is life-threatening (i.e., increases the risk of death at any time of the event); results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; and is considered clinically significant by the investigator.[2] After the ICF was signed, all SAE should be reported immediately to sponsor, in patient files and in the CRF.

Any AE/SAE that was unresolved at the patient's last AE/SAE assessment in the study was followed up in order to "control" it. The typically required information that I had to collect and then register in CRF was: event designation, start date, end date (if applicable), severity, causality, outcome, action taken with subject (*e.g.* concomitant medication) and with study drug (*e.g.* interruption, discontinuation), and if it was a SAE. If it was a SAE, the typically required information was: event designation, start date, end date (if applicable), severity, causality, outcome, action taken with subject and with study drug, serious criteria that categorized the event as serious, significant clinical tests, diagnostic procedures and lab parameters and a descriptive narrative of the event. In each new study visit, I prepared an ongoing AE/SAE list to discuss with investigator/subject. When the investigator and I followed the events, it was very important to provide the final outcome: completely recovered, recovered with sequelae, not recovered (i.e., ongoing), condition improving, or death.

The intensity (i.e., severity) of an AE was graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 and version 4.0.[26] Intensity of AE that were not included in CTCAE criteria were assessed based on the investigator's clinical judgment, using the following categories:[26-27]

- Grade 1 (mild) – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; and no disruption of normal daily activity;
- Grade 2 (moderate) – Moderate; minimal, local or non-invasive intervention indicated; discomfort sufficient to reduce or affect daily activity;
- Grade 3 (severe) – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling events that caused inability to work or perform normal daily activity;
- Grade 4 – Life-threatening consequences; urgent intervention indicated;
- Grade 5 – Death related to AE.

The causality relationship of study drug to the AE was assessed and categorized as below:[27]

- Not related – it does not follow a reasonable temporal sequence with study drug administration;
- Unlikely – reasonable temporal association with drug administration, but is more likely to have another cause which can explain the occurrence of the event;
- Possibly related – reasonable temporal association with study drug administration, but the event could also be explained by another cause;
- Probably related – reasonable temporal association with study drug administration and the event is more likely explained by the use of study drug than any other cause;
- Definitely related – reasonable temporal association with study drug administration and there is no other cause that can explain the occurrence of the event.

All AE/SAE that were related to study drug were designated as adverse reactions. When assessing the causality of the AE/SAE, alternative causes, such as subject medical history, underlying diseases, concomitant therapy, or other risk factors must be considered. Reporting possible adverse reactions is a very important task because it will help to identify AE that might be truly associated with study drug.

The notification of AE occurred in almost all clinical studies. The most common AE, per department, were:

- Cardiology – Anxiety, depression, hyperkalaemia, bleeding events, dizziness, and renal failure;
- Oncology – Paresthesias, asthenia, thrombocytopenia, anaemia, anorexia, dizziness, mucositis, alopecia, anxiety and depression;
- Infectious diseases – Anorexia, dizziness, anxiety, photosensibility reactions and rash;

In the endocrinology department only one AE was reported: dizziness. In the rheumatology department no AE were reported because, at the end of my curricular training, subject enrolment process had not yet been initiated. In respect to the notification of SAE, it occurred in eight studies, mainly caused by unplanned hospitalizations.

***Communication with sponsor, monitor and with the other elements of the research team and, if applicable, with regulatory authorities***

During my training, I had the opportunity to talk with three people who came to HIP on behalf of the sponsor. In the first case, the meeting was scheduled to present a new clinical study; the second situation was to congratulate the research team for the good performance; and the third occasion was to discuss possible recruitment strategies. The physical presence of a sponsor representative is not frequent. Monitors were the people who established the communication between research teams and sponsor.

The main channels to communicate with the monitor were telephone and e-mail. The use of letters and faxes were not so common, but they were also a valid alternative.

Whenever there was a question related to a clinical study, I contacted the monitor in order to help me to overcome/resolve the situation. Other types of communication included: re-order study material/lab material; request dry ice; report SAE; inform monitor of the study evolution (study status); receive/send study documents; receive and send responses/clarification of queries in paper format; send documentation related to subject payments; contact with other hospitals (*e.g.* subject hospitalizations/emergencies); contact with taxi services; contact with financial departments; contact with subjects and with other elements of the research team; collect study documents; prepare study visits, monitoring visits and, if applicable, audits; among others.

When a trial was closed, I had to send a notification letter to CEIC and other to the administration board of HIP in order to notify the clinical study completion to these entities. I perform this task once during my curricular training.

***Preparation of monitoring visits***

An important function that I performed for all studies from all departments was the preparation and follow-up of monitoring visits. The focus of these visits is to evaluate the way that the clinical study is being conducted and to perform source data verification (SDV) to ensure that all data collected were reliable and to ensure that reconstruction and evaluation of the study was possible. SDV is an evaluation of the conformity of the data presented in CRF with source documents.[2]

To prepare a monitoring visit or even during a monitoring visit, I had to:

- Identify a quiet place for the monitor to work;
- Enter all available and required data in subjects' CRF and resolve all open queries;
- If applicable, confirm that all SAE forms were submitted to sponsor and are available for review;
- Give monitor access to the ISF, patient files and patients clinical records (discharge notes, emergency records, concomitant drug prescriptions, among others);
- Organize, update and archive all source documents in subject files;
- Organize, update and archive all clinical study documents in the ISF;
- Confirm that all ICFs are well obtained and available for review;
- If needed, schedule an appointment for the monitor to visit the pharmacy;
- If needed, schedule an appointment for the monitor to speak with the PI/investigators;
- Be available to provide explanations/help when requested by monitor; be available to perform corrections in source documents, in the CRF or in other clinical study documents.

In these visits, it was possible to clarify questions from all involved parties. If possible, all outstanding issues were resolved during these visits. Four to five monitoring visits were appointed, at least, per month. All monitoring visits were prepared in advance to ensure that all required documents and files were present and organized.

***Coordination of study close out visits***

During my curricular training, I had the opportunity to attend one close out visit. In these visits, monitors come to the centres for the final review of regulatory files, SDV and drug accountability reconciliation; to resolve all open issues; to ensure that all study records are collected and archived; to collect all study drug, equipment and study materials. Some examples of tasks performed by me in the study close out visit that I attended are:

- Arrange a mutually convenient date and time for the monitor to conduct the close out visit;
- Ensure that all regulatory documentation, source documents and CRF were complete and available for review;
- Give access to all required documents to complete the close out visit to the monitor;
- Ensure that all queries had been resolved;
- Inform the monitor of the storage location of study records;
- Discuss the sponsor's requirements for subject follow-up for SAE after close out with the monitor;
- Identify points of contact for new issues that may arise, such as data queries or, if applicable, inspections.

During the curricular training period, I had the opportunity to witness, at least, two close out visits.

***Safeguarding GCP, protocol and applicable laws and regulations' adherence***

This important task has, as main objective, to ensure study compliance, which is defined, according to guideline ICH Topic E 6, as the "adherence to all the trial-related requirements, GCP requirements and the applicable regulatory requirements".[2]

All study-related visits, procedures or other clinical interventions should be done in compliance with study protocol, GCP requirements and with applicable regulatory requirements. Thus, I had to ensure that no protocol deviations were committed. If some unintended protocol deviations or non-compliance with GCP requirements or other applicable regulatory requirement occurred, I had to report them to the sponsor in order to take the appropriate action designed to prevent the recurrence of the detected deviation. Serious and persistent non-compliance by investigator or centre could justify the termination of investigator or

centre participation in the clinical study. During the period of my curricular training, a serious or a persistent non-compliance never occurred.

***Archiving study documents and maintenance of study documents updated and organised***

During my curricular training, I had the opportunity to maintain and update the study files. When a document was missing, it was assumed that it was not collected. For this reason, archiving all documents was fundamental to maintain study documentation updated and organized and avoid losing them. All study documents should be validated with signature and date and they should be carefully archived in the ISF, in the pharmacy file and/or in the patient files. This is mandatory to correctly conduct the study, to rapidly find a necessary document and to organize all study documentation to facilitate my daily work, monitoring visits and, if applicable, audits/inspection visits.

All unused files, superseded documents and all documentation from a finished study were stored in the Clinical Research Archive. This archive was established on January 2011 and it was developed to store all documentation related to clinical research. The clinical research archive is a restricted access room equipped with desks, chairs and stationaries. Files from studies already completed/finalized, files from studies prematurely stopped or files from studies not approved/started in HIP are all stored in this archive. The clinical research archive is also used to store other study material, like study kits or shipment material.

***Prepare study site payments***

A financial agreement is established between the sponsor, the PI and the study site. In this agreement, the terms of the conduction of the clinical study and the economic aspects related to the study are documented.[15]

In specific periods, the sponsor reimbursed the study site/PI, on a completed visit per subject basis and in accordance with the budget established in the financial agreement. When the HIP received a new study payment, I had to prepare a document where a discrimination of the amount that was transferred was presented: indirect costs associated with the payment and subjects and visits that were being reimbursed. After that, an Excel document was prepared and sent to the Financial Department of HIP. This Excel document contains the distribution of the total amount paid, based on the HIDP rules: indirect costs are always taken from the total amount and the remaining value is distributed between the institution (HIDP) and the research team.

The five tables below (Table 5 to Table 9) present a short description of the twenty clinical trials and the four observational studies that I followed during my curricular training, per medical department. Despite the fact that this information is available in ClinicalTrials.gov, in this report, study drug name and sponsor were not referenced in order to respect the confidential information of studies. The study drug name will be replaced by IP.

For all clinical studies, the first task performed was to carefully read the study protocol and analyse all related study documentation. This initial task was aimed to familiarize myself with study objectives, procedures and with some study specifications, such as: how to collect study samples, how to handle the study drug, and what forms the research team or I should acquire. This first approach was essential to coordinate the study appropriately.

When I began my curricular training, there were already five ongoing clinical trials in cardiology department, all from different sponsors: ATLAS 2, TIMI 50, CL3-16257-067, ENGAGE and ATMOSPHERE (Table 5). Later, two new clinical trials were proposed to HIP: TRILOGY and CL3-05985-018 (Table 5). All seven studies were phase III interventional studies. The new IP or the new combination of drugs was tested to treat different conditions. The therapeutic indications are presented in Table 5.

Table 5. Clinical trials followed in the cardiology department: study acronym, therapeutic indication, study intervention and study phase.

| Acronym | Condition | Intervention | Phase |
|---|---|---|---|
| **ATLAS** | - Acute Coronary Syndrome | - IP-1 (2.5 and 5 mg)<br>- Placebo | III |
| **TIMI 50** | - Atherosclerosis<br>- Ischemia<br>- Myocardial Infarction<br>- Cerebrovascular Accident | - IP-2<br>- Placebo | III |
| **CL3-16257-067** | - Chronic stable angina pectoris | - IP-3 (2.5, 5 and 7.5 mg)<br>- Placebo | III |
| **ENGAGE** | - Atrial Fibrillation<br>- Embolism<br>- Stroke | - IP-4<br>- Placebo<br>- Active comparator-1 | III |
| **ATMOSPHERE** | - Chronic Heart Failure | - IP-5<br>- IP-6<br>- IP-5 + IP-6 | III |
| **TRILOGY** | - Acute Coronary Syndrome | - IP-7<br>- IP-8<br>- Active comparator-2 | III |
| **CL3-05985-018** | - Essential arterial hypertension | - IP-9 + IP-11<br>- IP-10 + IP-11 | III |

According to Table 5, considering the first five clinical trials, they had already been approved when I arrived at HIP, so, when I began working with these trials they already had included subjects. However, I had also the opportunity to randomize subjects using the IVRS or IWRS for these trials. Considering the last two trials, they were proposed to be conducted in HIP during my curricular training. Thus, it was possible to coordinate their submission process. I followed these trials from their start, which allowed me to follow the screening and randomization of all subjects included and, consequently, allowed me to better understand the clinical trial since their initiation.

For ATMOSHERE, TRILOGY and CL3-05985-018, I agreed with the PI to schedule a weekly meeting to resolve all outstanding issues. For the other studies, these meetings were not so frequent but they also happened at scheduled moments. Beyond the resolution of all outstanding issues, these meetings were also useful to discuss subject recruitment, to collect missing documents, to overcome some existing problems, and to prepare monitoring visits.

It was also frequent to receive subject telephone contacts to confirm the date and time of study visits or to clarify some questions (*e.g.* how to use some specific study devices, how to take the study drug).

Except for the trial CL3-16257-067, I had to access to IVRS or IWRS in all studies to assign the subsequent study drug kit numbers. In these transactions, normally, the systems asked me to introduce some subject data. The outputs of the systems were the subsequent study drug kit numbers, always accompanied by a subject subsequent assignment confirmation fax or e-mail. All information provided by the system was registered in the study drug dispensation form and it was forwarded to the pharmacy, where the study pharmacist dispensed the study drug. Then, I confirmed the study drug kit numbers on the IVRS/IWRS and gave the study drug kits to the PI/sub-investigator.

For all studies presented in Table 5, I had to: prepare study visits, accompany visits, assign subsequent study drug, process and send lab samples, register all required data in CRF and update/archive all documents in patient files. For all studies, it was very important to follow the ongoing AE/SAE.

Regarding ENGAGE study, it was possible to participate in an investigator meeting, named “Re-Engagement & Retention Meeting”. This event occurred from 18$^{th}$ of May to 19$^{th}$ of May 2011, in London. The three main objectives of this meeting were:

- Maximize time on drug;
- Collect data on all subjects;
- Minimize withdrawn consent and lost to follow-up.

During the clinical study initiation activities, sponsor may hold an investigator meeting for a large number of study sites. These meetings aim to conduct study protocol and GCP principles training and to allow participants an opportunity to ask questions about clinical trial coordination and conduct.[16]

In oncology department, there were already four ongoing clinical trials (PETACC8, M10-300, SAVE-ONCO and TML) and two ongoing observational studies (FOCCO and GIDEON) when I began my curricular training. During my curricular training, three new clinical trials (TAGUS, REACH and MUTAR) and two new observational studies (REVEAL and SANTARÉM) were approved (Table 6).

According to Table 6, it is possible to verify that four clinical trials were phase III, two from phase II, one from phase IV and the other four were observational studies. These studies were from eight different sponsors. Therapeutic indications are presented in Table 6.

Table 6. Clinical trials and observational studies followed in the oncology department: study acronym, therapeutic indication, study intervention and study phase.

| Acronym | Condition | Intervention | Phase |
|---|---|---|---|
| **PETACC8** | - Colon cancer | - IP-12 + IP-13<br>- IP-13 | III |
| **M10-300** | - Advanced Colorectal Cancer<br>- Adenocarcinoma of Colon or Rectum | - IP-14<br>- Active comparator-3<br>- Active comparator-4 | II |
| **SAVE-ONCO** | - Prevention of Venous Thromboembolism<br>- Cancer | - IP-15<br>- Placebo | III |
| **TML** | - Colorectal cancer | - IP-16 + IP-17 /IP-18 or IP-17/IP-19<br>- IP-17/IP-18 or IP-17/IP-19 | III |
| **TAGUS** | - Metastatic colorectal cancer | - IP-20 + IP-21<br>- IP-21 | II |
| **REACH** | - Hepatocellular carcinoma | - IP-22<br>- Placebo | III |
| **MUTAR** | - Non-Small Cell Lung Cancer | - IP-23 | IV |
| **FOCCO** | - Colorectal cancer | Observational Study | - |
| **GIDEON** | - Hepatocellular carcinoma | Observational Study | - |
| **REVEAL** | - Colorectal Cancer | Observational Study | - |
| **SANTARÉM** | - Lung Cancer | Observational Study | - |

Working with clinical trials conducted in oncology department, gave me to the opportunity to work with two external imaging clinics. This permitted me to learn how to interpret a computerized tomography report, as well as how to interpret the Response Evaluation Criteria In Solid Tumours (RECIST) criteria, Version 1.1. RECIST criteria are “a set of published rules that define when cancer patients improve

(respond), stay the same (stable) or worsen (progression) during treatments".[28] These criteria are used in clinical trials with the aim of achieving a standardized way of assessing tumour response.

PETACC8 and FOCCO studies had CRF in paper format. Consequently, these were the only studies in which I could work with paper CRF. Nowadays, electronic CRF are better accepted and they have been replacing the paper CRF. Previously, the CRF pages were usually provided in duplicate. The original pages were monitored and collected by the monitor after I had registered all the required data and the copies of these original pages remained at the study site.

I only had the opportunity to assign the subsequent study drug kit numbers using IWRS for M10-300 and MUTAR.

PETACC8, SAVE-ONCO and TML were already in the follow-up period. In this situation, subjects were being followed without taking study drug and during this follow-up period, I had to prepare the follow-up visits and enter the required information on the CRF.

In February, it was possible to accompany the study close-out of SAVE-ONCO. In this visit, the monitor and I left the ISF organised and with all the requested documentation. ISF, patient files, pharmacy file, laboratory manual and all study documentation is identified with study name and is archived and stored in clinical research archive for fifteen years (some sponsors accept five to ten years). In these situations the administration board and CEIC were notified of the study completion with a formal letter sent to these two authorities.

REVEAL was a retrospective study, so it required a careful analysis of the patient clinic files in order to acquire and complete the required data in the CRF.

With SANTARÉM study, it was possible to work with three clinical scales: EORTC QLQ-C30, EORTC QLQ-C13 and MASCC antiemetics tool. EORTC QLQ-C30 and EORTC QLQ-C13 are questionnaires developed to assess the quality of life of cancer patients.[29] MASCC antiemetics tool is a questionnaire used to assess the prevention of chemotherapy-induced nausea and vomiting.[30]

For all the clinical trials presented in Table 6, except TAGUS and REACH, I had to: prepare study visits, accompany visits, assign subsequent study drug, process and send lab samples, register all required data in the CRF and update/archive all documents in patient files. For observational studies, I prepared the study visits, registered all required data in CRF and archived the documents in patient files. For all studies it was very important to follow the ongoing AE/SAE.

In endocrinology department, there was already one ongoing clinical trial: BI 1245.33. During my training, no more clinical trials were initiated in this department (Table 7).

BI 1245.33 was a phase IIb clinical trial to treat patients with type 2 Diabetes.

Table 7. Clinical trials followed in the endocrinology department: study acronym, therapeutic indication, study intervention and study phase.

| Acronym | Condition | Intervention | Phase |
|---|---|---|---|
| **BI 1245.33** | - Type 2 Diabetes | - IP-24 (10 and 25 mg)<br>- Placebo | IIb |

The tasks I performed in this trial were to: prepare study visits, accompany visits, assign subsequent study drug, process and send lab samples, register all required data in CRF and update/archive all documents in patient files. It was also very important to follow the ongoing AE/SAE.

Regarding the infectious diseases department, I had the opportunity to follow two clinical trials, since their start: BI 1241.21 and BI 1220.30 (Table 8). Both clinical trials were intended to treat chronic hepatitis C; one was phase II and the other phase III.

Table 8. Clinical trials followed in the infectious diseases department: study acronym, therapeutic indication, study intervention and study phase.

| Acronym | Condition | Intervention | Phase |
|---|---|---|---|
| **BI 1241.21** | - Chronic Hepatitis C | - IP-25 and IP-26<br>- Active comparator-5 and active comparator-6 | II |
| **BI 1220.30** | - Chronic Hepatitis C | - IP-27<br>- Active comparator-5 and active comparator-6 | III |

The tasks I performed in this clinical trial were to: prepare study visits, accompany visits, assign subsequent study drug, process and send lab samples, register all required data in CRF and update/archive all documents in patient files.

These two clinical trials gave me the opportunity to work with the infectious diseases department and with studies in the virology area.

With BI 1241.21 and BI 1220.30, I was faced with new challenges:

- Greater number of collection/transfer tubes – Usually, for other studies, the collection tubes never exceeded five tubes. In these trials, the collection tubes were about fifteen tubes per subject. For each type of tube/intended analysis the centrifugation process required different conditions: different revolutions per minute, different times of centrifugation and different times for blood clotting. This required me to carefully follow the lab/requisitions instructions when I was processing samples;

- More than one subject per day – This required me to carefully identify all subject documentation and lab materials; to grab attention when I was processing samples, that is, to grab my attention when I was transferring the plasma to transfer tubes, in order not to change the tubes and/or subjects;
- Frequent study visits – At some stages of these trials, subjects had to visit the centre more than once per week and this required that all documentation, patient files and CRF were updated and organised.

For these two studies, I had to: prepare study visits, accompany visits, process and send lab samples, register all required data in CRF and update/archive all documents in patient files. In these studies, I did not assign the subsequent study drug kit numbers because investigators were responsible for that task. For all studies, it was very important to follow the ongoing AE/SAE.

Study BI 1220.30 was audited in HIP. During my curricular training, I had the opportunity to follow and help the preparation for the audit. An audit is, according to guideline ICH Topic E 6, "a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOP), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)".[2] To prepare the audit, all patient files were organised and all subject related documents/forms were carefully archived; all required data was entered on the CRF and all open queries were resolved; the study drug dispensing logs were updated and the study drug accountability and compliance were performed; all missing study related documents were collected and archived; and the ISF was organised and updated.

In the rheumatology department, I had the possibility to follow a study program – OSKIRA Programme. This program was composed by three clinical trials: OSKIRA-2, OSKIRA-3 and OSKIRA-X (Table 9). These three trials were focused on the treatment of rheumatoid arthritis and they were all phase III.

Table 9. Clinical trials followed in the rheumatology department: study acronym, therapeutic indication, study intervention and study phase.

| Acronym | | Condition | Intervention | Phase |
|---|---|---|---|---|
| **OSKIRA Programme** | **OSKIRA-2** | - Rheumatoid Arthritis | - IP-28<br>- Placebo | III |
| | **OSKIRA-3** | | - IP-28<br>- Placebo | III |
| | **OSKIRA-X** | | - IP-28 | III |

At the end of my curricular training, subject enrolment process was not yet initiated. Thus, for these three trials, I just prepared study visit scripts, studied drug dispensation forms and nurse forms.

Regarding this study program, it was possible to participate in an investigator meeting, named "OSKIRA Programme". This event occurred from 6th of December to 8th of December 2010, in Barcelona. Its programme was composed by eleven themes: study protocols overview; medical monitoring, communication and surveillance; clinical monitoring; ICH-GCP guidelines; randomization and drug supply management via IVRS; IP management; central lab, imaging lab; AE reporting; cardiovascular events; and patient recruitment.

Meeting objectives were to:

- Provide the research teams with the rationale behind the OSKIRA Programme;
- Present a detailed understanding of the study protocol and the clinical research procedures that govern the study;
- Give the research teams an opportunity to interact with their colleagues and different study teams;
- Communicate the patient recruitment plan and to discuss best practice for patient recruitment and retention.

This was undoubtedly a very enriching experience. With this exhaustive explanation of study specifications and procedures, study teams became more able to correctly conduct a trial in their study sites, as they received training for the study by expert professionals and they had the opportunity to expose their particular questions.

At the end of my curricular training, on 30th of June 2011, three new clinical trials were approved by HIP administration board: DIGEST, BI 1220.7 and BI 1220.48. For these trials, I only worked in their formal approval process.

# *Chapter 4: Discussion*

When I began my training, ten clinical trials and two observational studies were already on-going at HIDP. During the training, ten new clinical trials and two new observational studies were approved by HIDP and were started. When my curricular training finished, three new clinical trials were approved. Sponsors see in HIP a potential clinical study site for three main reasons: (1) motivated and qualified staff; (2) adequate facilities and (3) adequate equipment and materials.

The creation of the clinical research archive was, frankly, one of the biggest endeavours of TRS. It allows us to efficiently archive all study binders. In the future, the creation of a documental management system will be important to guarantee the adequate files archiving/traceability.

During my curricular training, I identified some opportunities for improvement, as described below:

- Obtainment of ICF – The main errors detected in the ICF obtainment process are: incorrect ICF version provided to subjects and incorrect/incomplete filling of ICF. To correct these problems, I always **confirmed the ICF version**, as well as, **the adequate completion of all fields**.

- Subject recruitment – Nowadays, meeting the subject recruitment objectives is one of the main problems to overcome in Portuguese clinical research. This problem is justified for several reasons: patients that refuse to participate (cultural issues, family influence, unavailability); per investigator/site conditions (very optimistic estimative, demotivated research team, unavailability, inadequate logistic, internal conflicts); and per study protocol conditions (difficult study design, restricted inclusion/exclusion criteria, study procedures incompatible with clinic practice, very complex study procedures). So, to meet subject recruitment objective, I defined with investigators a **pre-selection list of potential subjects** at the beginning of the study, I **recorded all selected subjects, as well as all screening failures and the exclusion motive identified**. Databases search, such as patient hospital files or SAM application, was also a valid strategy that I adopted to improve recruitment.

- Study procedures – One of the most frequent problems detected during the study conduction is the failure to comply with study procedures required by the protocol. Thus, to overcome this situation, I always **prepared study visits in advance**. On the other hand, some study procedures are not performed within the time period established by protocol. So, I also **scheduled study visits in advance** to ensure that both parties, investigator and participant, will be available for the appointment.

- Clinical records – Incomplete, incorrect and, sometimes, the non-existence of clinical records are also frequently noticed. In clinical research it is often said "what is not written does not exist", so all study-related interventions, consultations or procedures reports should be recorded in patient files.. This problem comprises, as examples, the absence or incomplete source documents; minimalistic medical histories; AE/SAE records; concomitant medications. To overcome this problem I **prepared supporting documents for data collection**: checklists, study visit scripts, nurse forms, among others.

- AE/SAE notification – Usually, investigators tend to undervalue the events experienced by subjects – **under-reporting**. On the other hand, investigators fail to comply with reporting deadlines. Once again, I **prepared support documents** for the collection of AE/SAE information.

- Research team responsibilities – In this situation, I highlighted the delegation on unqualified personnel and personnel performing study procedures without having been delegated. This means that people who were performing study procedures were not familiarized with study protocol and, most likely, protocol deviations will occur. At the beginning of the trial, the **delegation log should be consciously filled** and **all research team should receive training** for the study. I remembered all research team in advance for the study appointments, in order to certify that all elements were available to perform their delegated activities.

During my curricular training, all health professionals of HIP have accepted my presence well and they have welcomed me as a collaborator of HIP, appreciating my work and entrusted me with responsibilities. However, I am faced with some difficulties:

- Managing many study visits at the same time – It happened frequently that study visits were scheduled for the same day. Managing many study visits at the same day/time became a complicated task, especially when they are from different studies. Whenever possible, study visits were scheduled for different days or, if it was not possible, for different times. In any case, when study visits coincided, I ensured that, at least, all required study procedures were complied. This exercise helped me to be more organised (developing a calendar of activities/tasks to accomplish in each day) and to prioritize more important and urgent tasks.

- Communication and linguistic skills – One of the biggest barriers that I faced was the use of English as the universal language. I had to use the English language in several occasions: to talk/communicate with sponsor, to contact with helpdesks, to activate my CRF/IVRS/IWRS access codes, to fill the CRF, to answer queries, among others. It was a good exercise that helped me improve my communication and linguistic skills.

- Personal and interpersonal skills – Due to my personal characteristics, the first contact with new people was another barrier that I had to overcome during the curricular training. At the beginning of the training, this difficulty was more evident because of the fear on how I would be received. At the end of the curricular training, this fear had diminished and the approach with other people was made in a more natural and spontaneous way.

Despite the highlighted difficulties, this was a very enriching training for many reasons. This training gave me the opportunity to:

- Better know the applicable laws and regulations better and to know how to apply them in my daily work;
- Apply the knowledge and tools acquired during the Master's degree;
- Work with different health professionals, with different backgrounds and expertise;
- Work with different sponsors and monitors;
- Work with a great diversity of trials, this is, trials with different study drugs, different therapeutic indications, different study phases, different specificities;
- Perform accompanied work and then to work autonomously;
- Improve my personal, interpersonal, social, search and linguistic skills.

# *Chapter 5: Conclusions*

Clinical research is absolutely essential to enhance progress in the health area. All elements of a research team are fundamental to study success and study coordinators are no exception.

The roles of the study coordinator are not perfectly defined yet. They are usually associated with data collection, but the contributions of these study elements can be far more extensive.

During the training, I had the possibility to follow all activities performed before, during and after the submission of a clinical trial to regulatory authorities. So, I believe that all curricular training objectives were fully achieved.

This was a very enriching curricular training for several reasons: gradual increase in autonomy (autonomous work); possibility to work with clinical trials in different interventional phases, different therapeutic indications and different required information/documents; possibility to work with different health professionals (physicians, pharmacists, nurses, laboratory technicians, diagnosis and therapeutic technicians) with different backgrounds and expertise; and possibility to work with different sponsors and monitors.

During the curricular training, I had the opportunity to perform a wide range of activities that were very useful to my growth as a professional. Being a study coordinator allowed me to apply all knowledge and tools acquired during the Master's degree and, especially, it allowed me to learn how to proceed in real work situations. Additionally, it was possible to identify my particular areas of interest, as well as to establish a working contacts network.

I have been invited to remain in HIP, continuing my functions as a clinical study coordinator. I really appreciated my journey in HIP and I am very thankful for the opportunity to remain a collaborator of this institution.

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