**Universidade de Aveiro** Secção Autónoma de Ciências da Saúde
**2013**

**MÁRCIA SOFIA BARBOSA CORREIA**

# RELATÓRIO DE ESTÁGIO EM COORDENAÇÃO DE ENSAIOS CLÍNICOS NO IPO-PORTO

# INTERNSHIP REPORT IN CLINICAL STUDIES COORDINATION AT IPO-PORTO

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Relatório apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Drª Manuela Adriana Leão Teles Seixas, Gestora Operacional da Unidade de Investigação Clínica do Instituto Português de Oncologia do Porto, e da Professora Doutora Maria Joana da Costa Gomes da Silva da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este trabalho *aos meus pais, a quem eu devo as minhas conquistas e grande parte daquilo que sou.*

**O júri**

president

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Professor Catedrático da Universidade de Aveiro

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**palavras-chave**

Coordenação de ensaios, Ensaios Clínicos, Medicina Farmacêutica, Investigação Clínica, Ensaios de Fase II, Ensaios de Fase III, Oncologia, IPO

**Resumo**

Este relatório descreve as actividades como coordenadora de estudos estagiária, na Unidade de Investigação Clínica (UIC) do Instituto Português de Oncologia do Porto (IPOP). Este estágio foi parte integrante das actividades curriculares do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

O estágio decorreu entre 21 de Janeiro de 2013 e 4 de Outubro de 2013, com o principal objectivo em adquirir experiência e especialização na coordenação de ensaios clínicos em oncologia.

No documento é apresentado o estado de arte de arte da investigação clínica com ênfase na actual situação em Portugal bem como em oncologia.

Na fase inicial do estágio realizei treino genérico em Boas Práticas Clínicas e sistemas de Captura de Dados Electrónicos e familiarizei-me com terminologia e sistemas classificação/avaliação próprios da área de oncologia para suportar as actividades de coordenação de ensaios clínicos no contexto dos protocolos de oncologia.

Na UIC, participei em vários estudos de fase II e III de 9 clínicas de patologia: Urologia, Ginecologia, Digestivos, Pulmão, Pele e Tecidos Moles, Cabeça e Pescoço, Onco-Hematologia, Mama e Pediatria. Dentro destas clínicas, participei intensivamente e adquiri mais autonomia nos ensaios clínicos da patologia de Digestivos. A clínica de Onco-Hematologia, agrega os protocolos de ensaios clínicos com procedimentos mais complexos.

Como coordenadora de ensaios clínicos pude participar intensivamente nas actividades de condução de um ensaio clínico, nomeadamente: Período de Randomização incluindo Rastreio e Randomização de doentes, Visitas Clínicas e Visitas de Monitorização.

A experiência adquirida ao longo do estágio curricular foi muito enriquecedora e permitiu-me adquirir capacidades e competências profissionais e interpessoais e aprender a enfrentar situações inesperadas, desenvolvendo estratégias para lidar com as mesmas. Para além disso possibilitou-me a consolidar e aplicar os conhecimentos teóricos adquiridos no Curso de Mestrado nas diferentes fases de coordenação dos estudos.

Em conclusão, ao longo do estágio adquiri competências, motivação e experiência para enveredar por uma carreira na área de investigação clínica, especialmente como Coordenadora de Ensaios Clínicos.

**keywords**

Coordination of Clinical Trials, Clinical Trials, Pharmaceutical Medicine, Clinical Research, Phase II Clinical Trials, Phase III Clinical Trials, Oncology, IPO

**abstract**

This report describes my activities as study coordinator (SC) intern, at the "Unidade de Investigação Clínica" (UIC) in the Oncology Portuguese Institute of Porto (IPOP). This training occurred during the second year of the Pharmaceutical Biomedicine Master at the University of Aveiro.

My internship took place between 21st January, 2013 and 4th October, 2013 with the main objective to gain experience and expertise in oncology coordinating clinical trials.

I present the state-of-the-art of clinical research with emphasis on current situation in Portugal as well as in oncology.

At the beginning of internship I performed generic training in Good Clinical Practices (GCP) and *Electronic Data Capture systems* and familiarised myself with terminology and classification/assessment systems regarding the oncology area to support the clinical trial coordination activities in the context of the oncology protocols.

In UIC, I participated in 6 phase II and 25 phase III clinical trials of 9 clinics of pathology: Urology, Gynaecology, Digestive, Lung, Soft Tissue and Skin, Head and Neck, Onco-Haematology, Breast and Paediatry. Within of these clinics, I intensively participated and acquired more autonomy in clinical trials of the Digestive pathology. The Onco-Haematology clinic includes the more complex procedures of the clinical trials protocols.

As SC, I could intensively participate in the conduction clinical trial activities, namely: Randomisation Period, including Screening and Randomisation of patients, Clinic Visits and Monitoring Visits.

The experience gained during my curricular internship was very enriching and enabled me to acquire professional and interpersonal skills and competences and to face unexpected situations, developing strategies to deal with them. Additionally, it was possible to consolidate and apply the theoretical knowledge acquired during Master Course in Pharmaceutical Medicine at different stages of clinical trials coordination.

In conclusion, during my curricular internship, I gathered the competences, motivation and experience to pursue a career in clinical research, particularly, as SC.

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# Abbreviations

| | |
|---|---|
| **AB** | Administration Board |
| **AE** | Adverse Event |
| **APIFARMA** | Associação Portuguesa da Indústria Farmacêutica |
| **CEIC** | Comissão de Ética para a Investigação Clínica |
| **CNPD** | Comissão Nacional de Proteção de Dados |
| **CPI** | Critical Path Initiative |
| **CRA** | Clinical Research Associate |
| **CRF** | Case Report Form |
| **CRO** | Contract Research Organisation |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CV** | Curriculum Vitae |
| **EC** | European Commission |
| **ECG** | Electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group<br>Common Terminology Criteria for Adverse Events |
| **eCRF** | electronic Case Report Form |
| **EORTC** | European Organisation for Research and Treatment of Cancer |
| **EU** | European Union |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practices |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IDCT** | Investigator-Driven Clinical Trial |
| **IMI** | Innovative Medicine Initiative |

| | |
|---|---|
| **INFARMED** | Autoridade Nacional do Medicamento e Produtos de Saúde I.P |
| **IP** | Investigational Product |
| **IPOP** | Instituto Português de Oncologia do Porto |
| **ISF** | Investigator Site File |
| **IVRS** | Interactive Voice Response System |
| **IWRS** | Interactive Web Response System |
| **MS** | Member State |
| **MS p.c.** | Manuela Seixas personal communication |
| **NCE** | New Chemical Entity |
| **PI** | Principal Investigator |
| **R&D** | Research and Development |
| **RECIST** | Response Evaluation Criteria In Solid Tumours |
| **SAE** | Serious Adverse Event |
| **SC** | Study Coordinator |
| **SF** | Screening-Failure |
| **SOPs** | Standard Operating Procedures |
| **UIC** | Unidade de Investigação Clínica |
| **USA** | United States of America |

# 1. Introduction

My internship within the scope of the Pharmaceutical Biomedicine Master´s degree, at the University of Aveiro, took place at the "Unidade de Investigação Clínica" (UIC) of "Instituto Português de Oncologia do Porto" (IPOP), from January 2013 to October 2013.

The training report contemplates the clinical trial coordination activities developed in the UIC of IPOP. It is organised into five chapters. The chapter 1 - Introduction, contextualises my training and comprises a characterisation of the host institution primary and secondary training objectives my view of the state-of-the-art on the clinical research, addressing the current situation of clinical research in Portugal and in the oncology field. The content of this topic will be initiated with a brief approach to the clinical research in humans. Then, it will be addressed the global pharmaceutical Research and Development (R&D), where it will be focused the current difficulties, challenges and the strategies inherent to the pharmaceutical R&D process. Furthermore, it will be addressed the clinical trials classification based on study objectives and the current situation of clinical trials in Portugal, which will include the clinical trials regulatory framework, the sector characterisation, barriers and challenges and finally the strategies to improve the clinical trials activity. The last subtopic contemplates the recent data about the clinical oncology research on an European and National scope. The chapter 2 - Generic Training, presents the online training courses and my acquaintance with support tools in the context of clinical trials protocols. The chapter 3 - Specific Training, describes the clinical trial coordination activities according to the stage of clinical trial (initiation, conduction and closeout) that I experienced during my internship. The chapter 4 - Discussion, presents a critical view about my training experience. Finally, the chapter 5 - Conclusion, draws attention to the final considerations also resulting from my experience.

## 1.1 Overview of the Host Institution

### 1.1.1 Instituto Português de Oncologia do Porto

IPOP is a highly differentiated institution that belongs to the National Health Service. The mission of this institution is to provide health care services, timely, patient-centered, not neglecting the prevention, research, training and education in the oncology scope with the goal of ensuring high levels of quality, humanism and efficiency (6). IPOP was transformed in an "Entidade Pública Empresarial" by the Decree-Law nº 233/2005, of December 29th (7).

Over the last years, the IPOP has performed an extensive investment in research (8). The Research Centre is a research unit recognised by Foundation for Science and Technology since 2004 (9). The general and long-term objective of Research Centre is the understanding of the pathobiologic mechanisms behind carcinogenesis, which ultimately will help improve the cancer prevention and/or treatment (10). Currently, this centre has the following structure (9, 10): the Cancer Genetics Group; the Cancer Epigenetic Group; the Molecular Oncology Group; the Experimental Pathology and Therapeutics Group; the Medical Physics and Radiation Protection Group and the UIC where I developed the majority of activities during my internship. The UIC will be presented, hereinafter, in more detail.

The Tumour Bank, inaugurated in 2012 and located in the Service of Pathological Anatomy, will be a major support service for the cancer research (11). This functional unit enables, after a previous written authorisation by the patient, the harvest of tumour tissue samples which then are stored and used for biomedical research (11).

The Portuguese Oncology School of Porto provides education and professional integration of its students and professionals in the area of oncology, medicine, health and other complementary areas (12).

Following it will be presented in detail the UIC, the unit of the IPOP devoted to the clinical trials.

### 1.1.2 Unidade de Investigação Clínica

During my internship in IPOP, I developed the majority of activities as Study Coordinator (SC) in UIC.

The UIC was created on the year 2006 (13). The first main goal was to support the existing clinical trials and to promote the implementation and the execution of new clinical trials and also to ensure the compliance with respective protocols and procedures (4, 13).

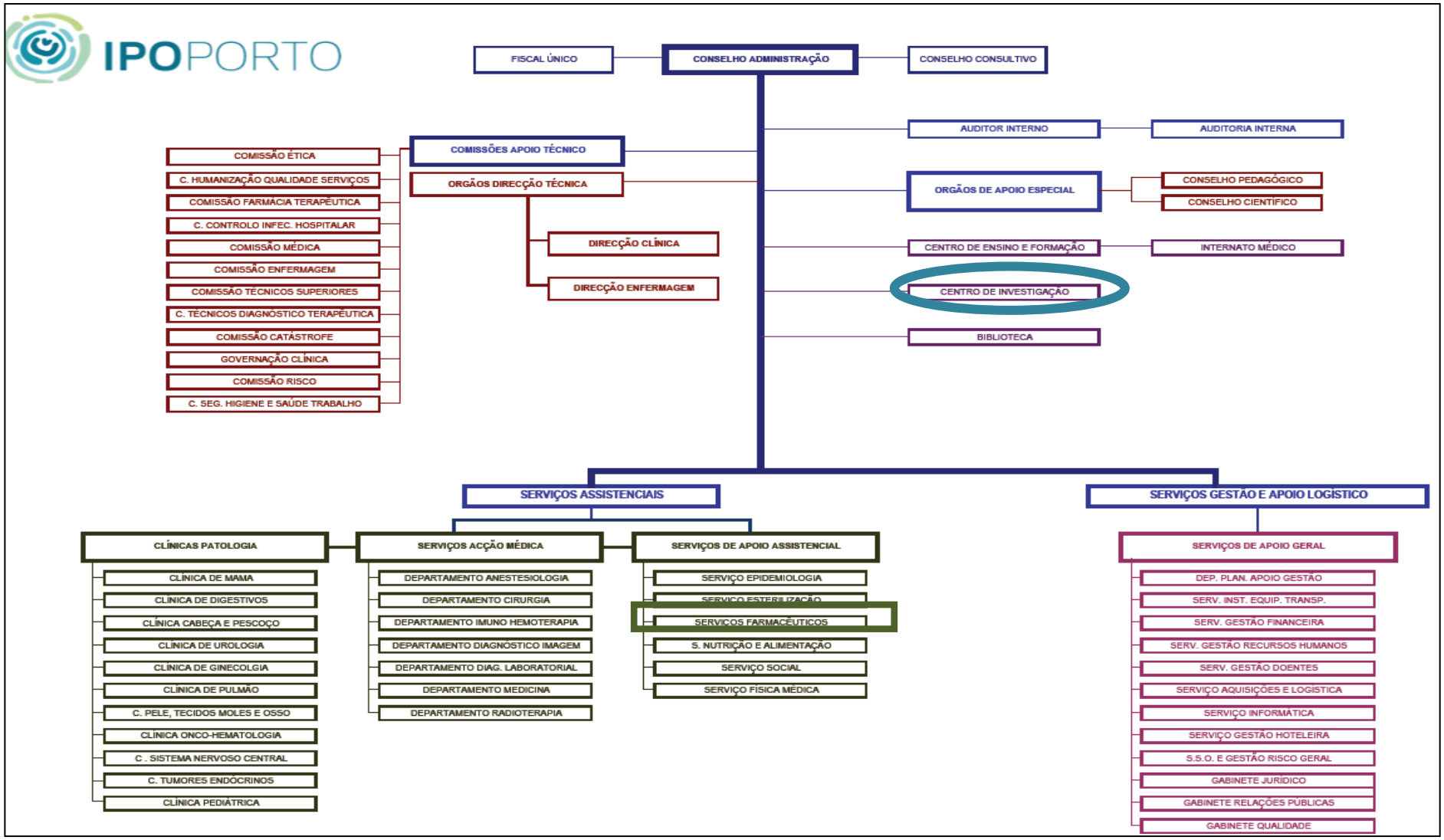



**Figure 1: The Organigram of the IPOP [adapted from(2)].**
*The" Unidade de Investigação Clínica" is depicted in the oval figure.*

Therefore, to continue to pursuit the main goal established at the beginning, it was necessary to create the unit´s team not only to maintain the support and execution of clinical trials but also to attract new and best global clinical trials (4, 13). It started with one single responsible SC, and due to the results it increased to a team of 4 full time SCs [(Manuela Seixas personal communication) (MS p.c.)]. These members were divided by pathologies. Each SC was responsible for a specific group of pathology clinical trials (MS p.c.). On this way of work, each investigator's team had its own SC and could develop a close work relation and also achieve the clinics objectives (MS p.c.). This strategy proved to be effective for achieving each clinical trial main objectives, gaining competitiveness between different teams and motivating a progressive growth of the number of recruited patients as well as of the clinical trials (see figures 2 and 3) (4, 13).

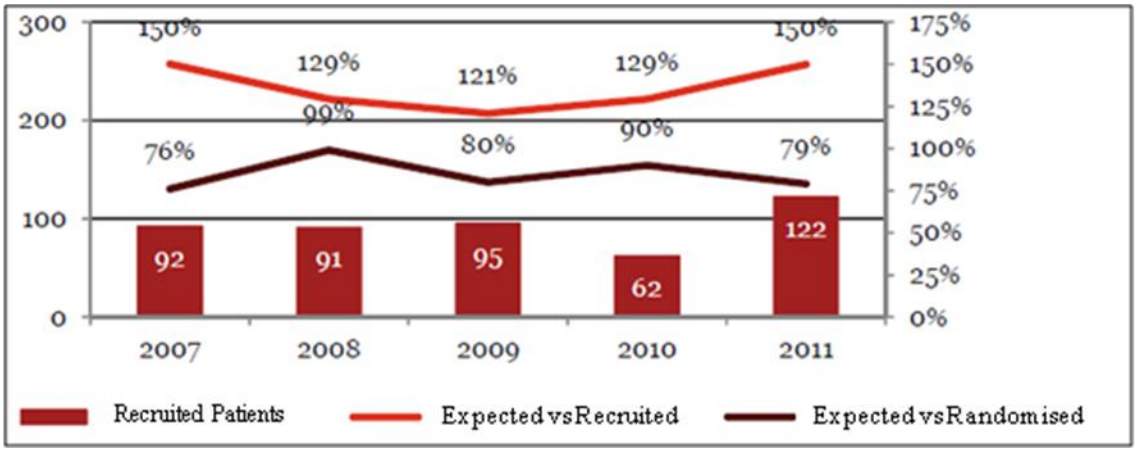



**Figure 2: Clinical trials recruitment rate in UIC of IPOP between 2007 and 2011 [adapted from (4)].**

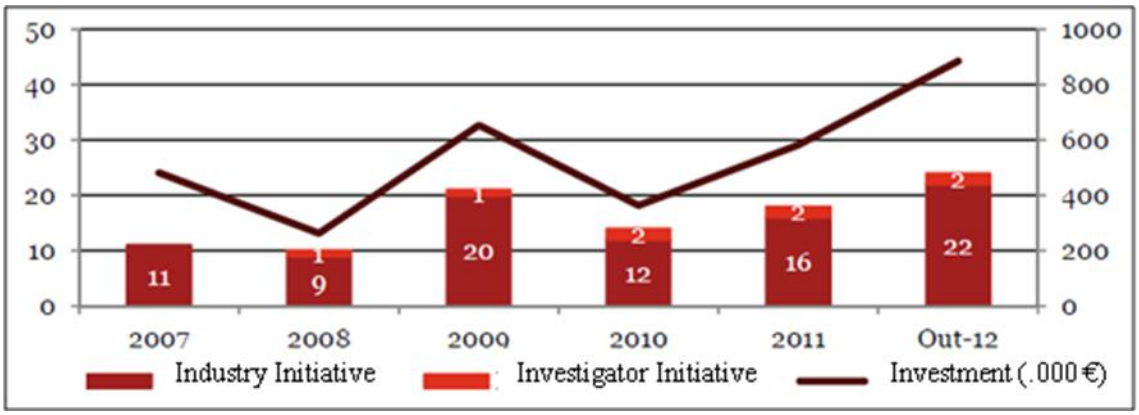
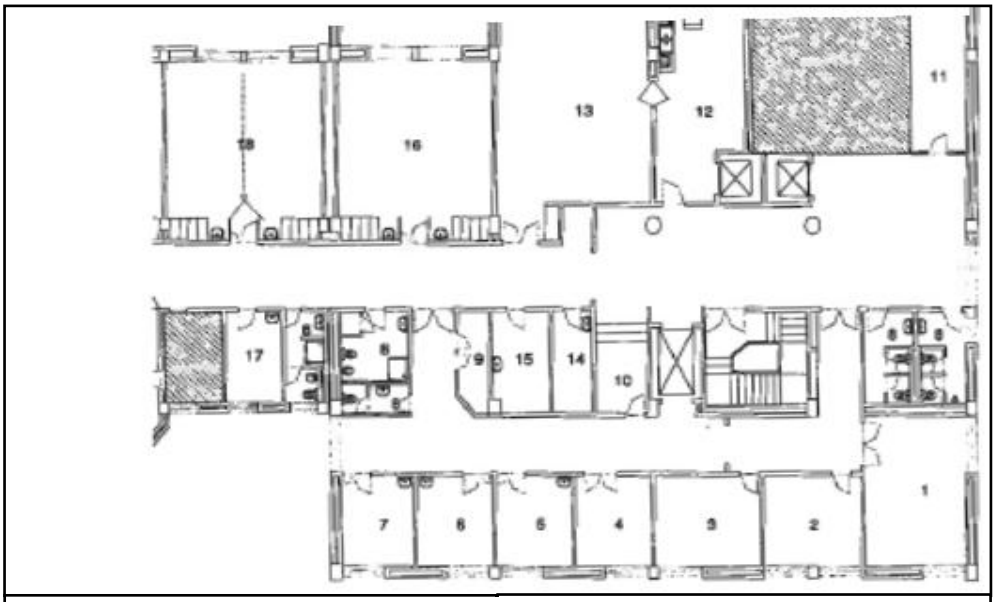



**Figure 3: Authorised clinical trials in UIC of IPOP between 2007 and 2012 [adapted from (4)].**

This work lead not only to the growth of number of SCs, as it led to the increase of the number of infrastructures and facilities (3). In the beginning, there was a single room for the 4 SCs and today there is a main infrastructure where each SC has its own office (3). Currently, the UIC has the following infrastructures (3):

- 9 rooms (offices), 3 monitoring rooms, 1 meeting room, 2 file (archive) areas (see figure 4) and 1 area of pharmaceutical services (clinical trials pharmacy);




**Legend**

1: Office (Manager of GCP and Quality)
2: Office (Operational Manager)
3: Office (Financial Manager)
4: Office (SC)
5: Office (SC)
6: Office (SC)
7: Office (SC)
10: Office (Reception)
11: Office (Financial Manager Assistant
13: Meeting Room
15: Monitoring Room 3
16: File (archive) area
17: Monitoring Room 2
18: Monitoring Room 1

**Figure 4: Current plan of UIC [adapted from (3)].**

The pharmaceutical facilities (clinical trials pharmacy) are not represented in figure 2 because they are located in another building of IPOP. They are represented in the figure 1 at the green square.

The human resources of UIC is represented in the figure 5 and involves 1 Medical Coordinator of UIC, 1 Manager of Good Clinical Practices (GCP) and Quality, 1 Operational Manager, 1 Financial Manager, 5 Study Coordinators, 4 Clinical Trial Assistants, 1 Financial

Manager Assistant, 1 Administrative and 2 Operational Assistants (1). Briefly, each UIC team member is responsible for (1):

- Medical Coordinator represents the IPOP and technically assists IPOP Administration Board (AB), concerning clinical trials; proposes a Plan of UIC Activities and respective report to the AB; ensures the synchronisation with the several departments and services of IPOP involved in clinical trials and evaluate the educational needs of the team members and their performance;
- Manager of GCP and quality proposes, develops and maintains the GCP System; proposes to the AB the Annual Plan and performs the Internal Audits; participates in the support team to the external audits and inspections and reviews the support documentation to the submission to the IPOP AB;
- Operational Manager manages UIC's daily activities and coordinates the activities of each UIC member; prepares, submits and accompanies the "Dossier of Approval Request to the conduction of a clinical trial at IPOP"; reviews, periodically, the records of clinical trials procedures and informs the UIC Financial Manager, to allow the billing to the sponsor and prepares and participates in the support team to the internal and external audits and inspections;
- Financial Manager evaluates, reviews and emits a financial opinion regarding the clinical trials financial protocols; interacts with the Financial Services, Pharmaceutical Services, UIC and sponsors to the bills emission regarding the services and procedures of the clinical trials protocols and complies with the procedure respective to the compensation of clinical trial participants' travel expenses, in accordance with financial protocol;
- SCs implement clinical trials, supporting the clinical trial team in every activities related with the preparation and organization of the procedures and documentation; ensure that the clinical trial team complies with the GCP and with the clinical trial protocol; participate in the Investigator's meetings; maintain the clinical trial documentation up-to-date and archived, complying with the sponsor procedures; maintain the clinical trial procedures registry updated; schedule and give support to the monitoring visits; comply with the procedure respective to the compensation of clinical trials participants' travel expenses, in accordance with financial protocol and update the information about each clinical trial status, reporting it internally and to the sponsor;
- Clinical Trial Assistants assist the SC on her activities, namely the archive of documents and its update, and scheduling the participants visits and exams;
- Financial Manager Assistant assists the financial manager on her activities;

- Administrative supports the UIC team on every activity related with clinical trials, namely the preparation and internal distribution of clinical trials documentation and material; receives and distributes every correspondence and clinical trial material in the UIC, and dispatches to the exterior and controls and ensures the availability of the material necessary to the UIC functioning;
- Operational Assistants transport the participant health records from other services to the UIC and vice-versa, as needed; track the patient health records location and update its registry and prepare the monitoring offices for each visit with the adequate material.

Thus, IPOP is a reference research centre to the clinical trials conducted in Portugal in the majority of pathologies treated in the institution (13). In coming years, UIC expects to maintain a sustained growth of performance and promote the participation in clinical trials of earlier phases, with the creation of a specific unit to phase I clinical trials (13).

The operationalization of the work of UIC was achieved in accordance to its own regulation and procedures that all team members are aware of (1). The UIC performed its own Standard Operating Procedures (SOPs) to equalise the work of all SCs (14). In terms of revenue sharing, it was created a model that promotes the reinvestment in clinical research through a fund of support to independent projects (4).

Before the creation of UIC, the IPOP had already established partnerships not only with important national and international biopharmaceutical industry and also with academic institutes that performed clinical trials and promoted the investment in clinical research in general, contributing also to support the independent investigators of own trials (4). The European Organisation for Research and Treatment of Cancer (EORTC) is an example as well as several cooperative groups, such as: Lung Cancer Group, Digestive Portuguese Group and Breast Cancer Group (4), (MS p.c.).

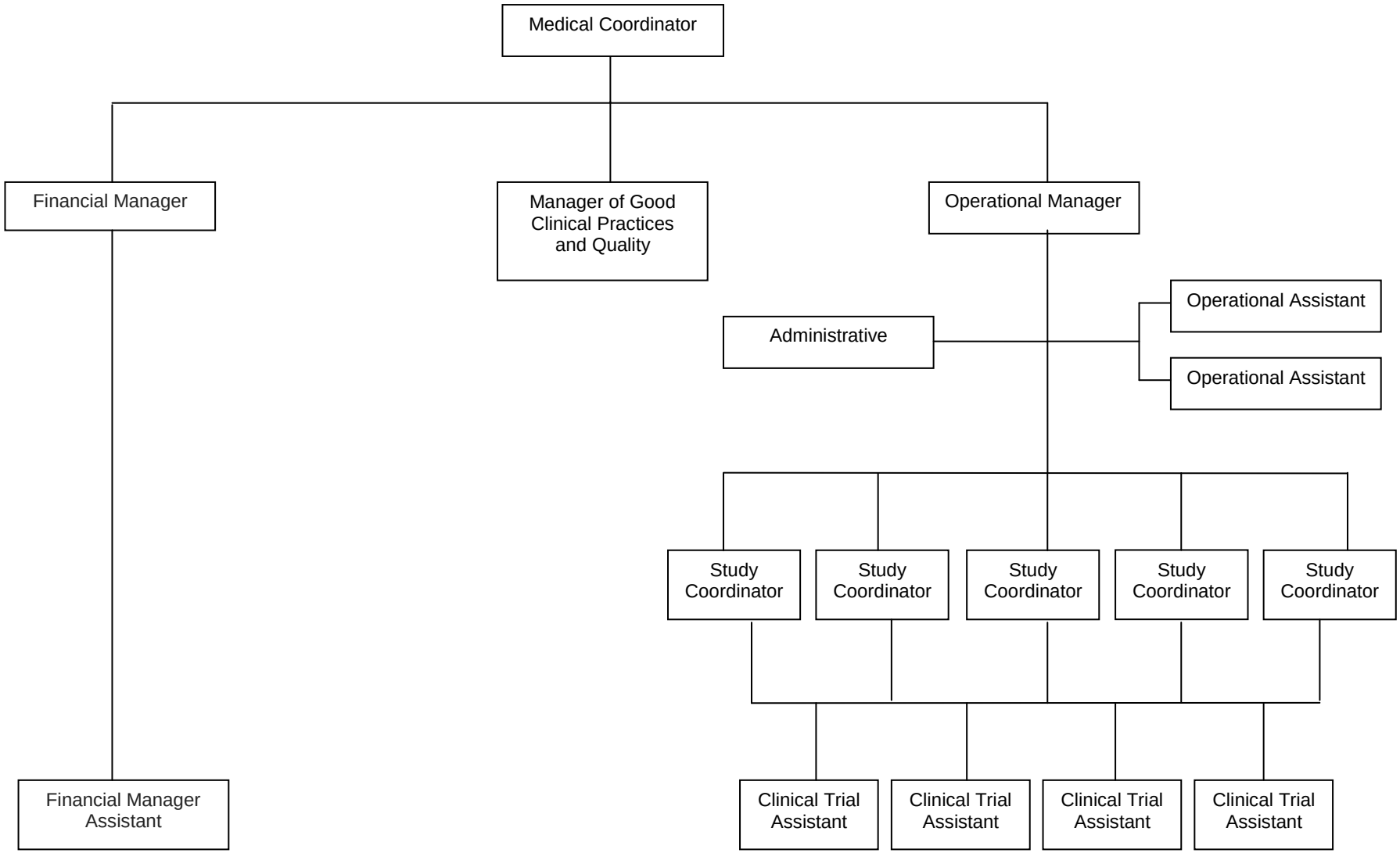



**Figure 5: The Organigram of UIC [adapted from(1)].**
*The Administrative and the Operational Assistants* assist all team members but are under the purview of the *Operational Manager.*

## 1.2 Training Objectives

During my Biomedical Sciences Degree and Master´s Course in Pharmaceutical Medicine, in University of Aveiro I acquired learning tools and knowledge which, together with my expectations about the work of a SC, allowed establishing my primary and secondary training objectives. The host institution, the UIC of IPOP, also had influence in the objective's definition.

Thus, through my curricular internship, I intended to adjust my work in order to achieve the following objectives:

### 1.2.1 Primary Objectives

- To gather skills, experience and know-how in clinical studies coordination;
- To understand the procedures associated to the operation of a clinical research centre;
- To gain experience and expertise in oncology clinical research;
- To consolidate and apply on the job the knowledge acquired during the Biomedical Sciences Degree and the first year of Master´s Course in Pharmaceutical Medicine.

### 1.2.2 Secondary Objectives

- To participate and gather comprehensive understanding in all coordination phases of a oncology clinical study;
- To deepen my understanding in oncology clinical research protocols;
- To acquire autonomy to perform the activities associated with clinical trials and observational studies coordination;
- To develop interpersonal skills that contribute to a good professional performance in the clinical studies coordination – assertiveness, proactivity, working in a multidisciplinary team and problem solving;
- To establish a professional contact network, cooperating with distinct professionals like physicians, study nurses, pharmacists, Clinical Research Associate (CRA), and other professionals whose activities are daily or frequently associated with the SC in the clinical studies conduction;
- To contribute to the improvement of clinical research in UIC.

## 1.3 State-of-the-art of the Clinical Research

Clinical research is the investigation with human subjects that is (15):

- Patient-oriented research: It is performed in human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) (15, 16). It involves a direct interaction between the human subject and the investigator (15, 16). It may include mechanisms of human disease, therapeutic interventions, clinical trials or development of new technologies (15, 16);

- .Epidemiological and behavioural studies: They enable to assess distribution of disease, factors that affect health, and how people make health-related decisions (15, 16);

- Outcomes research and health services research: They seek to identify the most effective and most efficient interventions, treatments, and services (15, 16).

Results from clinical research are used to decide the diagnostic, to treat or make a prognostic of pathologies (17). In addition, the conduction of clinical research in humans includes strict scientific guidelines and legal and ethical principles to protect the volunteers. The activities related with clinical trials are conducted in a trial site. This site may be a public or private institution, a laboratory or other entity with adequate human and material resources to conduct a clinical trial in national territory or other Member State (MS). In my opinion it seems important to have a structured, qualified and trained team, including GCP managers, operational managers, healthcare professionals, SCs, technical assistants, among others to improve the performance of clinical trials activities and consequently improve the effectiveness, safety and quality of clinical research.

Only through clinical research, it is possible to gain insights and answers about the safety and effectiveness of treatments. It is important to recognise that scientific advances in this area was possible only due to the participation of volunteers, both healthy and those diagnosed with an illness. Therefore, clinical research requires complex and accurate testing in collaboration with communities affected by the disease (18).

Improving the overall capacity of the clinical research centre will depend on ensuring an appropriate infrastructure in place to support the investigators, volunteers and institutions that organised and carry out the trials (19).

### 1.3.1 Overview of the Global Pharmaceutical Research & Development

Pharmaceutical R&D is the process of discovering, developing and launching new drugs to the market. The discovery process comprises all early research to find a new drug candidate and testing it in the lab (20). At the end, researchers expect to have a promising candidate drug to test in humans (20). During the development process, the candidate drug must undergo extensive studies in humans and must prove to be safe and effective before it is approved by regulatory entities (20). This process involves conducting clinical trials with specific goals and requirements and it is organised into distinct phases that will be addressed in more detail, in the section 1.3.2 “Clinical Trials Classification”.

The research-based biopharmaceutical industry has provided a crucial contribution to the European health and economy (21). For decades, the R&D process has led to the increase of the number of new drugs that have been approved and marketed (21). The increase in R&D of new drugs has coincided with the constant growth of biopharmaceutical industry in Europe through augment in productivity, contributing to the Europe’s balance of trade and employability (21).

However, currently, the R&D process is facing some difficulties (21). Global R&D expenditure in the pharmaceuticals and biotechnology sector has steadily increased, without a corresponding output in new medicines that reach the market and the patients, as it is represented in the figure 6 (21). The number of new drugs defined by the new chemical entities (NCEs), approved by year, has not kept pace with the R&D costs (21). According to the data of figure 6, despite the progressive increase of R&D costs, the number of NCEs approved has decreased extensively between 1995 and 2004 (21). Currently, this trend has remained and became unsustainable (22).

The R&D of a new drug is a long, resource-intensive and complex process. According to the estimates, the costs to bring a new molecule to the market are around €292 million ($400 million) and €658 million ($900 million) between the period 1994 to 2000. The current trend has been a significant raise in this value (5, 21).

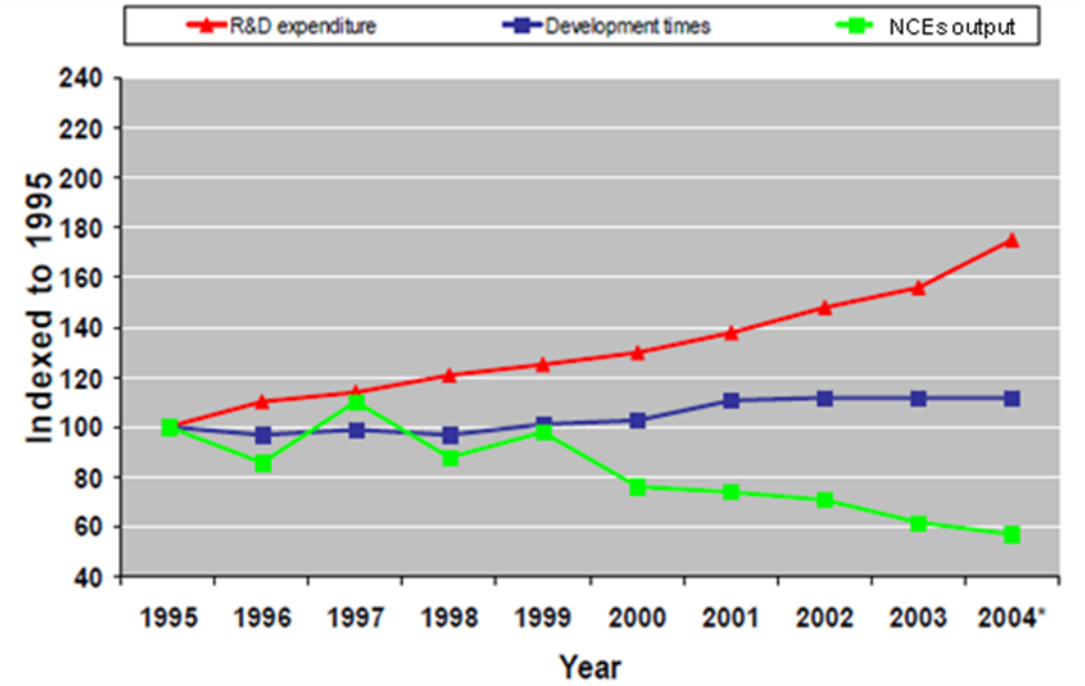



**Figure 6: Global R&D expenditure, Development times versus New Chemical Entities (NCEs) approved (1995-2004) [adapted from(5)].**
*The more recent data is not entitled to free access.*

Furthermore, despite of the long time to the R&D of a new drug (10-15 years), there is a high possibility that this drug will fail to reach the market (5, 20). This is the major reason for concern, also identified, as a bottleneck. Data about attrition rates indicates that the probability of a drug candidate passing from pre-clinical stages (the first stage of laboratory study on toxicity) to market commercialization is 6% or less (5, 20). The reasons to the failure of R&D process are the lack of efficacy (25%), clinical safety concerns (12%) and toxicological findings in pre-clinical evaluation (20%) (5).

Currently, European clinical research is facing some challenges related with escalating and unsustainable drug development costs, high failure rates, pharmaceutical R&D is moving out of Europe, public spending on health R&D is a fraction and is stagnating compared to the USA, private sector spending on R&D is becoming increasingly spent in the United States of America (USA), and is increasing risk adversity among investors (21). Therefore, scientific breakthroughs are not translated into the expected results, and research efforts are fragmented (21). In this context, it is important to recognise the phenomenon of clinical trials globalisation and its implications to the pharmaceutical R&D over the world (23). Clinical trials are moving out of developed countries in regions like Western Europe and USA to be conducted in developing countries such as Eastern Europe, India, South America, and China (23). A reason behind the globalisation is cost savings due to lower salaries of physicians,

nurses and SCs in emerging countries. In addition, clinical trials in emerging countries are attractive due to the high population sample ("large pool of potential research participants") that ensures an accelerated recruitment rate, simplified and cheaper regulatory environment, foster positive relationships among investigators and answer questions of concern throughout the world (23). This will contribute to increase the returns invested in pharmaceutical R&D (23). In this way, it is crucial to streamline regulations in order to reduce redundancy while ensuring ethical conduct (23).

In order to bridge the bottlenecks in the R&D process of new medicines, two international initiatives have been developed to revolutionise the conventional drug development paradigm and support the faster discover and development of better and innovative medicines (5). These initiatives are *Critical Path Initiative* (CPI), from USA and *Innovative Medicine Initiative* (IMI) from Europe.

*"The CPI is a strategy of Food and Drug Administration (FDA) to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured"* (24). This initiative was intended to highlight the need for collaborative efforts of all stakeholders (federal agencies, patient groups, academic researchers, industry, healthcare practitioners, and others) in order to increase the efficiency, predictability, and productivity in the development of new medical products (5). Thus, CPI is based in 6 topics that address specific tools, techniques and methods to improve the candidate drug's performance. The topics are synthesised in the table 1 (24, 25).

**Table 1: Brief description about CPI topics [adapted from (25)].**

| Topic | Description |
|---|---|
| **Biomarkers development** | Biomarkers would improve the efficiency of product development; help identify safety problems before a product is on the market. They can reduce uncertainty by providing quantitative predictions about performance and also can revolutionize product development for a disease group. |
| **Streamlining clinical trials** | To improve the design and conduct of a clinical trial to increase the efficiency of product development. These trials define and measures the variations in individual responses→ **Personalized Medicine**. |
| **Bioinformatics** | An application that permits analyse biological data about patients, with the goals of creating robust, quantitative computer models of normal human physiology, of the natural human history of certain diseases and of the course of a disease affected by standard treatments. |
| **Manufacturing** | Tools that help to identify and to analyze critical products to improve efficiency and quality in manufacturing. |
| **Antibodies and countermeasures to combat infections and bioterrorism** | Methods that help rapid pathogen identification and better predictive disease models. |
| **Developing therapies for children and adolescents** | To improve methods for predicting if treatments will work in children and adolescents are combined and analyse data from existing paediatric studies. |

The IMI results of collaboration of public and private sector between large and small biopharmaceutical, healthcare companies, regulators, academia and patients (5). The IMI proposes paths to the faster discovery and development of more effective innovative medicines with fewer side-effects enhancing Europe's competitiveness. This initiative establishes 4 pillars that address the bottlenecks in the current R&D process (5). The topics are presented in the table 2 (5).

**Table 2: A brief description about the pillars of IMI [adapted from (5)].**

| Pillar | Description |
|---|---|
| **Predictivity of Safety Evaluation** | 9 recommendations to improve the predictivity in safety evaluation and benefit - risk assessment with regulatory authorities. |
| **Predictivity of Efficacy Evaluation** | 9 recommendations to improve the predictivity pharmacology, the identification and validation of biomarkers, patient recruitment and benefit - risk assessment with regulatory authorities. |
| **Knowledge Management** | 15 recommendations including the establishment of a Translational Knowledge Management and the creation of a Knowledge Management Platform to break the bottlenecks related to gaps in information technologies. |
| **Education and Training** | 5 recommendations addressing the bottlenecks related to gaps in expertise in biomedical R&D knowledge and skills. Implementation of multidisciplinary programmes to develop skills. |

Recently, on 10 July 2013, the European Commission (EC) released its proposal for the IMI 2 that it is expected to start in 2014 (26). The IMI2 addresses the major challenges currently facing the European healthcare system, the pharmaceutical industry and the regulatory framework together with research required to attend them (26). *"The aim of IMI2 is to enable an appropriate European-level research and innovation response that will make a crucial contribution to delivering better health and wellbeing for all, and positioning Europe as a leader in the rapidly expanding global markets for health and wellbeing innovations" (26).* The vision of IMI 2 is to deliver the right treatment to the right patient at the right time for priority diseases, supporting the personalised medicine and prevention (26).IMI 2 will drive a new and integrated approach on R&D that it will be concretised through the cooperation between all sectors within the healthcare ecosystem (26). Thus, IMI2 focus the creation of new biomedical public private partnerships between the pharmaceutical industry and the European Union (EU) (represented by the EC) that will facilitate the engagement and coordinated co-operation between all key stakeholders in the provision of healthcare today

such as healthcare practitioners, regulators, patients and payers to ensure new scientific advances are translated into innovative, effective products, strategies, interventions and services (26).

### 1.3.2 Clinical Trials Classification

According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic E6 (R1) – Guideline for GCP, a clinical trial or clinical study is defined as "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), 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" (27).

Clinical trials are commonly classified into 4 temporal phases (Phase I-IV). However, the temporal phases do not imply a fixed order of studies. Thus, it is preferable the classification based on study objectives: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use. The clinical trials classification consists of (28):

- Human Pharmacology: Typically these studies are associated with phase I and they start with the first administration of investigational product (IP) in humans with non-therapeutic objectives, including initial safety and tolerance assessment, pharmacokinetic and pharmacodynamic definition, and drug metabolism and drug interactions determination (28). Usually, these studies are conducted in a small population of healthy volunteers (20-100), except in case of drugs with potential toxicity, that are carried out in patients (28).

- Therapeutic Exploratory: Typically these studies are associated with phase II and they are conducted in a group of patients (100-500 patients, selected by moderately narrow criteria which leads to homogeneous population) with the disease under study to investigate the therapeutic efficacy (28). Another goal is to determine the dose and regimen for subsequent studies (phase III) (28). Additional objectives are to evaluate potential endpoints, target population and methodologies for confirmatory studies (28).

- Therapeutic Confirmatory: Typically these studies are associated with phase III and they are conducted in a larger patient population (1000-5000) to demonstrate or confirm therapeutic benefit (28). These studies are intended to confirm the evidence accumulated

during phase II (safety and effectiveness to the evaluation of overall benefit-risk profile of the treatment) and provide a basis for marketing approval (28).

- Therapeutic Use: Typically phase IV Studies are conducted after the drug approval - after demonstration of the drug's safety, efficacy and dose definition - and are related to the approval indication. They are not required for approval, but are intended to optimise the drug's use (28, 29).

### 1.3.3 Current Situation of Clinical Trials in Portugal

The presence of regulatory framework in Portugal includes both an EC directive and Portuguese legislation. Therefore, in Portugal, the conduction of clinical trials on medicinal products for human use according to the GCP is governed by the legal regime established by Law nº 46/2004, of August 19th, which is transposed into the national law through the Directive nº 2001/20/EC of 4 April 2001 of the European Parliament and of the Council (30). The regulation of these aspects in a harmonised way through international (ICH) and community level ensures the integration by guidelines and quality requirements that govern the conduction of clinical trials (30). The main goal is to protect the subjects who participate in the research. Recently, the legislation is compiled in the volume 10 (*The rules governing medicinal products in the European Union*) of EudraLex (30, 31).

Clinical research in Portugal has been losing its position in the context of global investment in health (4).

Since 2006, the number of clinical trials submitted and authorised has been steadily declining. The lowest value was reached in 2011, with 88 studies (4). Phase III clinical trials have a great expression in Portugal and represent about 68% of clinical trials number approved in 2012 (4). The completion of phase I clinical trials is almost null, only 8 studies were authorised over the last 4 years (4). According to the data of INFARMED the predominance of treatments covered by authorised clinical trials corresponds to the antineoplastic and immunomodulating agents, anti-infectious agents and central nervous system agents (32). The number of new patients enrolled has been declining, with exception in 2011 (4). The study "Ensaios Clínicos em Portugal (Potencial de Investimento)", conducted by "Associação Portuguesa da Indústria Farmacêutica" (APIFARMA) concluded that, between 2007 and 2011, It was only 70% of patients initially planned were recruited (4). The average approval times of a clinical trial exceed 70 days between 2009 and 2011 (4). This time does not include the approval by administration of the trial site which is essential to

start the study and can take several months. The regulatory entities responsible to the clinical trial approval process are “Autoridade Nacional do Medicamento e Produtos de Saúde I.P” (INFARMED) that authorises the conduction of clinical trial (4, 33); “Comissão de Ética para a Investigação Clínica” (CEIC) which provides an opinion in to conduct the clinical trial and “Comissão Nacional de Proteção de Dados” (CNPD) that authorises the health data processing performed in the context of the clinical trial (4, 34, 35).

In Portugal, the majority of clinical trials is promoted by multinational pharmaceutical companies (4). The Investigator-driven clinical trials (IDCTs) are scarce when compared with other European countries, like Spain and United Kingdom(4) .

In this way, clinical research in Portugal is facing barriers which have contributed to the loss of country’s competitiveness in attracting these activities (4). In 2013, APIFARMA summarised these barriers (4) namely:

- Policy and Strategy of the sector: The clinical research activities are not recognised as strategies to the improvement of health care neither to the national economy. There is no development strategy due to the lack of adaptation of the regulatory framework to the requirements of activities such as, inefficient funding mechanism, incentives to improve the trial sites conditions, creation of research networks and promotion of independent research. Additionally, there is a negative reputation of clinical trials.
- Regulation and Legislation: The time required for clinical trials approval is long and usually exceed the statutory period of 60 days for application approval by regulatory entities, referred above. The financial contracts do not follow a standardised structure and its approval by hospital administrations is also a lengthy process and it can take several months. There is not defined specific legislation to the public disclosure of clinical trials. In addition, the volume of clinical trials promoted by investigators, IDCTs, is greatly reduced, due to the lack of a legal framework that regulates and promotes this initiative.
- Organisation and Infrastructures: Hospital administrations do not recognise the potential strategic of clinical research. There is a lack of appropriate infrastructures that drives to the inefficiency of centre as well as a poor cooperation between key stakeholders.
- Incentives, Training and Career: The failure in financial incentives diminishes the availability of professionals to participate in clinical trials activities that are not valued for the purposes of career advancement. The academic degree in health care area not provides a deep basis in clinical research. Additionally, there are no full conditions, such as financial systems, partnerships and support to promote and perform IDCTs.

- Technology and Information: Despite of the “Plataforma Nacional de Ensaios Clínicos” creation, the information access about clinical trials is very limited, scattered and hamper the interaction between different stakeholders.

Therefore, the success of clinical research in Portugal will depend on the definition, and implementation of initiatives in order to overcome the obstacles referred above, as well as, the recognition of clinical research potential to Portugal (4). Examples of initiatives are: review of current legislation on the clinical trials approval process and review of funding programs and incentive systems for clinical research (4). Currently, the regulatory framework for clinical trials in Portugal is undergoing a revision. There is a proposal for a regulation of European Parliament and of the Council on clinical trials on medicinal products for human use that repeals the Directive nº 2001/20/EC (36). The reasons for this proposal are related to the unsatisfactory results of clinical research during the last years (36). Thus, this new proposal addresses these results and barriers in order to combat them and improve the clinical research. Despite of this scenario, the IPOP is an institution engaged in promoting and fostering the activity of clinical trials in Portugal (4, 13). According to the data of figures 2 and 3 since its creation, the UIC of IPOP assumed a progressive and sustained growth at different levels (4). This activity has been an opportunity to the patients, ensuring the access to the innovative treatments with potential beneficial health effects (4).

### 1.3.4 Current Trends in Clinical Oncology Research

Recent data from the EU (27 countries) point that in 2008, 2.5 million people were diagnosed with cancer that is the second most common cause of death (29% of deaths for men or 3 out of 10 deaths, 23% for women or 2 out of 10 deaths) (37). This scenario is expected to increase due to the aging population (37).

The most common types of cancers in the EU were colorectal, breast (most common in women), lung (most common in men) and prostate cancers (37).

Despite progress over the past 10 years, cancer remains a key public health concern and a huge burden on European societies (5). The treatment of several cancers is inadequate and it is urgent to improve all aspects of the cancer research, from prevention to translational and clinical research (5). The main problem of cancer treatment is the lack of quality systemic treatments (5).

Currently, almost half of the NCEs in clinical development are directed against cancer targets, like bevacizumab, cetuximab and trastuzumab (5). In addition to the high-risk of these plans, there is lack of disease-related biomarkers to sustain early decision-making on products (5). The IMI emphasise the need of collaboration in cancer research, and its success “is dependent on close working relationships with major cancer organisations such as the EORTC, other national cancer bodies and the major cancer charities” (5). The ambitious goal established by *Commission Communication on Action Against Cancer: European Partnership* is to reduce the cancer incidence by 15% until 2020 (5, 37).

In this context, in Portugal the majority of clinical trials are promoted by multinational pharmaceutical companies of R&D and the main area of health involved is the oncology representing 40% of the total (4, 38).

Recently, it was initiated the clinical trials with the first Portuguese drug for oncologic patients (39). The action mechanism of this oncology treatment is based on the photodynamic therapy, a form of treatment of the tumours, cancers and other deformations of the tissue, using light and photochromic compounds in combination with the oxygen contained in the tissue (39). LUZ11 is the code name of the Portuguese drug for treatment of cancer (39). This is a good example to strengthen the clinical research in Portugal, in the oncology field.

# 2. Generic Training

At the beginning of my internship, I performed the ICH/CGP online training course and acquired the certificate in GCP. This training was organised into different modules and at the end of each module, I answered to some questions related with the content of the respective module. After to the course modules completion, there was a final assessment which consists of a reasonable number of multiple choice questions in order to evaluate the learning level acquired during the course. This course is an essential resource required to conduct all activities related to the clinical trials. In addition to this course, I also performed online training courses on *Electronic Data Capture* systems, namely in *Medidata Rave*®, *InForm* ™ and *Oracle® Clinical Remote Data Capture Onsite"*. The table 3 presents a brief description of each *Electronic Data Capture* system.

**Table 3: Brief description of *Electronic Data Capture* systems used during the internship (40-42).**

| System | Description |
|---|---|
| ***Medidata Rave®*** | Web tool for capturing, managing and reporting clinical research data, designed by efficiently streamlining the clinical trial process (41). |
| **InForm ™** | Internet-based tool selected for use on clinical trials to enter clinical data into the electronic case report forms (eCRFs) (40). |
| ***Oracle® Clinical Remote Data Capture Onsite*** | Web application that works with studies defined and designed using Oracle Clinical platform. RDC Onsite is used to collect, review, and report clinical data collected during a patient visit in a clinical study (42). |

These courses had a similar structure to the ICH/GCP course. They were divided into distinct modules with intermediate assessments at the end of each module, and a final assessment. The courses completion was an essential support tool to the introduction of clinical data in Case Report Form (CRF). Consequently, this is one of the many activities of a SC that will be addressed, in more detail, in the next section.

Additionally, it was required to acquaint me about theoretical tools in order to support my clinical trial coordination activities in the context of the oncology clinical trials protocols. Its knowledge was essential to understand, organise and execute activities, procedure and

tasks regarding the clinical trial protocol. These tools are the *Eastern Cooperative Oncology Group* (ECOG*)* Performance Status, the *Common Terminology Criteria for Adverse Events* (CTCAE) code and the *Response Evaluation Criteria In Solid Tumours* (RECIST) *criteria* and the Cancer Staging.

ECOG Performance Status (see table 4) is a scale and criteria used by physicians to evaluate the disease status of patients (if it exists progression), by the level though which disease is affecting the daily living activities of the patient (43).

**Table 4: The ECOG Performance Status (43).**

| Grade | Description |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| **2** | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **3** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| **5** | Dead |

The CTCAE code is a descriptive terminology used for Adverse Event (AE) reporting (44). There are two different and main CTCAE codes used for classification of AE: the version 3.1 and actually the version 4. Each clinical trial protocol defines the version for AEs classification. For each AE term is provided a grade that refers to the severity of the AE (see table 5) (44).

**Table 5: Description of AE Grades [adapted from (44)].**

| Grade | Severity |
|---|---|
| **1** | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| **2** | Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental *Activities of Daily Living*. |
| **3** | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care *Activities of Daily Living*. |
| **4** | Life-threatening consequences; urgent intervention indicated. |
| **5** | Death related to AE. |

The RECIST criteria are a set of rules that define the response of cancer patients to the treatment. Thus, it is possible to assess when patient improves ("responds"), stays the same ("stable") or worsens ("progression") (45).

The Cancer Staging describes the severity of the same in a patient according to the size and/or extent of the original tumour, and whether cancer has spread in the body (46). The common elements considered in the majority of staging systems are (46): site of the primary and the cell type - corresponds to the cells kinds found in cancer tissue; tumour size and/or extent (reach); regional lymph node involvement - the spread of cancer to nearby lymph node; number of tumours - the primary tumour and the presence of metastatic tumours, or metastases; tumour grade - how closely the cancer cells and tissue resemble normal cells and tissue.

# 3. Specific Training

## 3.1 Clinical Trials Coordination

Clinical trial coordination involves a vast number of activities and processes. The SC has a critical role in the clinical trial implementation, supporting the clinical trial team in every activity related to the preparation and organisation of the procedures and documentation.

As IPOP is structured by clinics such as: Urology, Gynaecology, Digestive, Lung, Soft Tissue and Skin, Head and Neck, Onco-Haematology, Breast, Paediatry, Endocrine Tumours, Nervous System, the several clinical trials are worked on these clinics (47). During my internship, I participated in phase II clinical trials in digestive, lung and soft tissue and skin pathologies and several phase III clinical trials as presented in table 6.

**Table 6: Clinical trial phases and number according to the clinics of pathology in which I was enrolled (48).**
*The list is available online.*

| Clinics of Pathology | Number of Clinical Trials per Clinics of Pathology and Phase | |
|---|---|---|
| | Phase II | Phase III |
| **Urology** | -- | 4 |
| **Gynaecology** | -- | 4 |
| **Digestive** | 2 | 1 |
| **Lung** | 1 | 2 |
| **Soft Tissue and Skin** | 2 | -- |
| **Head and Neck** | -- | 2 |
| **Onco-Haematology** | -- | 10 |
| **Breast** | -- | 2 |
| **Paediatry** | 1[1] | -- |

[1] Phase IIb

I will present the clinical trial coordination activities according to the stage of clinical trial - initiation, conduction and closeout of a clinical trial. I performed the conduction activities in all clinics of pathology and an initiation activity in the Onco-Heamatology clinic. Then, in the table 7, it is summarised the specific tasks (according to the stage of clinical trial) executed in each protocol regarding the clinic of pathology. Finally, it is described in detail the experience that I gained during my internship.

**Table 7: Synthesis of Clinical Trials Coordination Activities and Tasks performed in each Clinic of Pathology**

| Clinical Trial Coordination Activities and Tasks | Clinical Trial Coordination Tasks versus Clinic of Pathology | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Urology | Gynaecology | Digestive | Lung | Soft Tissue and Skin | Head and Neck | Onco-Haematology | Breast | Paediatry |
| **Initiation** | | | | | | | | | |
| Initiation visit | -- | -- | -- | -- | -- | -- | X | -- | -- |
| **Conduction** | | | | | | | | | |
| Recruitment Period: | -- | -- | X | X | -- | -- | -- | -- | -- |
| Screening; | -- | -- | X | X | -- | -- | -- | -- | -- |
| Randomisation of patients; | -- | -- | X | X | -- | -- | -- | -- | -- |
| Clinic Visits: | X | X | X | X | -- | -- | -- | -- | -- |
| Schedule of visits; | X | X | X | X | X | X | X | X | X |
| Preparation of Visits; | X | X | X | X | X | X | X | X | X |
| Patient's visit; | X | X | X | X | X | X | X | X | X |
| Documents, CRFs and AEs Report; | X | X | X | X | -- | -- | -- | X | -- |
| Packaging and Sending biological samples; | X | -- | X | X | X | -- | -- | -- | -- |
| Other activities performed after the visits; | X | X | X | X | X | X | X | -- | X |
| Patient's Discontinuation; | -- | X | X | X | -- | -- | -- | -- | -- |
| Monitoring visits | X | X | X | X | -- | -- | -- | -- | -- |
| Emergency Code Break | X | -- | -- | -- | -- | -- | -- | -- | -- |
| **Closeout** | | | | | | | | | |
| --- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

## 3.2 Clinical Trial Initiation Activities

Next, I will present the initial activities and procedures that involve a clinical trial, namely, the signature of a confidential agreement, assessment of the site conditions through the completion of the feasibility questionnaire, pre-trial qualification visits, analysis of financial contracts, clinical trial approval, investigator meeting an the clinical trial initiation visit to prepare the site to conduct the study.

### 3.2.1 Assessment of new Clinical Trials and Pre-Trial Visits

The sponsor or Contract Research Organisation (CRO) delegated is responsible for selecting the suitable sites to conduct the clinical trial (27). In the IPOP, the study is proposed directly to the UIC (MS p.c.). The UIC acknowledges the study to two elements: the director of the clinical service where the study is going to be performed and the clinic pathology director that will appoint the principal investigator (PI) and will lead the recruitment plan (MS p.c.).

The initial preparation of a new clinical trial involved the signing of a confidentiality agreement.

- Signature of Confidentiality Agreement: Confidentiality agreement or non-disclosure agreement is ensures the confidentiality of information and it is established between the PI and CRAs of the study. The agreement is signed to guarantee that both parties agree with the information addressed in the document (49). The operational manager of the institution is responsible to send the signed and dated confidentiality agreement by PI to the CRA (MS p.c.).

- Assessment of the site conditions: The assessment of site conditions may be done through the conduction of pre-trial visits and completion of the feasibility questionnaire.

- Pre-trial Visits: The purposes of these visits are to review the site adequacy, the training and experience of the study staff, the access to target patient population, and the site's interest in the clinical trial (MS p.c.). In IPOP, the representatives appointed by sponsor are to evaluate the site conditions are accompanied by the coordinator of UIC, the manager of GCP and quality, the operational manager and by investigator (MS p.c.).

- Feasibility Questionnaire: The feasibility questionnaire is an assessment tool that contains a specific questionnaire of the study to determine the incompatibility or viability of

promotion or implementation of the same in the site (50). This questionnaire enables to obtain the data about the target disease, potential for patients' recruitment, infrastructures and facilities of the site and also regarding human and material resources (50). In IPOP, the professional responsible to answer to this questionnaire is completed by the service director, the clinic pathology coordinator or the appointed PI. It must exist an understanding between these 3 intervenients (MS p.c.).

- Financial Contracts Analysis (review and signature): The financial contract must be reviewed and signed. This document sets the terms of clinical trial completion, the conditions of its provision and the economic aspects to be agreed between the sponsor and site (49). This contract contains direct and indirect costs of study, the payment period and all conditions established between the parties (49). The IPOP uses own template with payment percentages to the research team members. In UIC, the manager of GCP and quality is responsible to discuss and review the main points of document with CRA (MS p.c.). After reaching an agreement, it is submitted to the IPOP Administration Board (AB) and CEIC (MS p.c.).

- Clinical trial Approval: According to the ICH-GCP (27) and the Portuguese legislation (Law nº 46/2004, of August 19th) (51) , the conduction of a clinical trial requires a prior approval of INFARMED, CEIC and CNPD. After the study approval by regulatory authorities, the preparation of clinical trial submission to the IPOP AB (MS p.c.). The submission file involves the compilation of several documents and signatures, such as: curriculum vitae (CV) of the PI; financial contract signed and dated by the sponsor/CRO and PI (MS p.c.). CV identification of the sponsor, study synopsis, study protocol, investigator brochure, informed consent, insurance certificate, clinical agreement and study authorisation by service director, study approval by regulatory authorities and materials to be used during the study are included in the submission dossier (MS p.c.). After a last review of the dossier sent by the sponsor/CRO and by the manager of GCP, the approval is sent to the operational manager (MS p.c.). This team member is responsible for gathering the internal approval of the financial manager and a letter of accordance of the medical coordinator of UIC (MS p.c.). Then, the dossier will be sent to the IPOP AB for final approval (MS p.c.). Thus, the implementation of clinical trial in the institution depends on the final and favourable opinion of AB (MS p.c.).

During my internship, I did not have the opportunity to actively participate in all these activities. However, I am acquainted with the same because I had an oral session, in which, it was explained to me the following topics:

- What is involved in each of these activities;
- The order in which they occur;
- The professionals of the institution which collaborate in these activities;
- Some particularities applied to the institution.
- This explanation allowed was important to consolidate the sequence of activities and what activities are performed to get the clinical trial approval.

### 3.2.2 Investigator's Meeting

An investigator´s meeting is a meeting organised by the clinical trial sponsor, or its representatives and attended by investigators and site personnel who have agreed to participate in the multi-centre clinical trial (52). In this working session the investigators are informed about the pharmacology of the investigational medicinal product and it is provided updated clinical information of compound (52). The main purpose is to ensure the understanding of the protocol, study design and other clinical trial procedures, as well as to foment consistency in protocol compliance and clinical trial procedures among sites. In addition, this meeting is also important because (52):

- It ensures that everyone involved in study receives the same information;
- It enables training in therapeutic area and specific review of the protocol and associated documents, like eCRFs;
- It provides to the site personnel - that in the UIC may involves, the investigators, operational manager and SCs – the opportunity to discuss study logistics and to meet key sponsor (CRA's, project managers, medical officers, among others).

During my internship, I did not have the opportunity to participate in an investigator´s meeting. In despite of this, I received the feedback of UIC team members that already participate in several meetings. They explained me about the specific contents covered in these sessions (eligibility criteria, recruitment, safety concerns) and emphasised the opportunity to clarify doubts related to the protocol and establish professional relationships. In addition, they also sensitised me to the SCs participation in these sessions because the

knowledge acquired will contribute to conduct the study activities with more accuracy and security.

All these steps described were explained to me by my supervisor in a formal meeting. However, I did not the opportunity to perform or accompany them, perhaps because of the level of specialisation of tasks at UIC in IPOP.

### 3.2.3 Clinical Trial Initiation Visit

Clinical trial initiation visit is required to prepare and set up the site to conduct the study. The main purpose of this visit is to ensure that clinical trials will be conducted under the suitable conditions. This visit involves a meeting with investigators, SC, pharmacists, study nurses among other elements of research team. It is conducted by a sponsor representative, usually a CRA. During the internship I had the opportunity to attend an initiation visit and follow the procedures before, during and after the visit. This visit occurred in the ambit of a clinical trial of Onco-Haematology clinic.

The first step before the visit was to schedule an appropriate date, time and place with CRA and research team. Until the visit date, some essential documents were being prepared, obtained and filed. These documents included the CVs of research team and signature of the financial disclosure. During this time, some study trainings were completed by research team members and the certificates were filed. In addition, I tried to understand the key aspects related to the protocol and I read the protocol synopsis.

In this visit, the CRA initiated its presentation after confirming the presence of expected research team in the room. Throughout the meeting, the CRA review the following items (27, 53):

- Study protocol: objectives and study design, study-specific procedures and skill sets (imaging schedule and modalities, electrocardiogram (ECG) time points), inclusion and exclusion criteria, recruitment (strategies and targets) and timelines, protocol amendments;
- Investigational Product: dispensing, preparation, administration and unblinded procedures;
- Laboratory Procedures: supplies (central lab kits, manuals, shipping materials, patient folders), sample collection, processing and shipping requirements and central laboratory considerations (transmission of lab results);

- Records: screening and recruitment logs, drug accountability and dispensing logs;
- Data Collection: eCRFs;
- Safety Reporting: Serious Adverse Event (SAE) and AE;
- Training: It was specified the training needs of research team members and addressed, if required, the hypothesis of additional training prior to initiate the study.

During and after the presentation, the research team had the opportunity to discuss these items and also clarify relevant doubts related to the study. At the end of presentation, SC delivered some documents to be signed by team members such as, delegation signature log and visit log, among other essential documents.

After conclusion of these procedures, the visit took place in UIC, only between SC and CRA. The purpose was to provide relevant study supplies, check the organisation of clinical trial materials operational equipment (electrocardiographs) in UIC and organise the documents in the Investigator Site File (ISF). The study supplies provided were the electrocardiographs (including training CD and manual), imagiology manuals, patient cards, study medication diaries and administrative binders. The SC was informed about the randomization, medication assignment, completion study medication diaries, SAE and AE reporting procedures, CRFs and source documents. Then, the CRA provided the way to create the passwords for eCRF and Interactive Web Response System (IWRS). This password belongs to the respective SC and cannot be shared.

Furthermore, the CRA was also to the clinical trials pharmacy to supply some materials and train the professionals. CRA was also in the local lab with study nurse to supply the central lab kits, manuals, shipping materials, patient folders and to clarify some sample collection procedures. This visit can be performed in one or more days. The sponsor/CRO schedules the visit with team members required in order to train properly the team members. After this visit completion, the site is ready to initiate recruitment strategies and begin enrolling patients.

## 3.3 Clinical Trial Conduction Activities

### 3.3.1 Recruitment Period

During this period, the investigators have the opportunity to recruit the patients for the study (49). The expected number of patients to include in the study and recruitment timeline is specified in the initiation visit.

During my internship, my contribution to the patient recruitment was through the consultation of clinical processes of patients which had been recently admitted in a clinic of pathology of the IPOP. Thus, together with other SC, I read the clinical data of patients and checked, according to the eligibility criteria, if patient met any inclusion and/or exclusion criteria. When I found a patient that met one or more inclusion criteria and no exclusion criteria, I warned the responsible SC and this patient was signalised. Throughout this process, I only analysed the inclusion and exclusion criteria that I was able to understand. All these criteria are then verified by the PI or sub-investigator in order to recruit the patient.

The majority of contribution to the patient's recruitment is done by PI and co-investigators of study during the group consultations, external consultations and emergency service. I did not have the opportunity to attend a group consultation (during which it is decided the treatment for a patient), however, the SC of UIC may participate and contribute to find eligible patients. When an investigator finds a potential patient to include in a study in any external consultation or group consultation, he/she contacts with the SC in order to request an informed consent. Then, the SC goes to the consultation and delivers the informed consent, the main inclusion/exclusion criteria and also the flowchart of events to investigator which provides an explanation about the same (emphasising essential aspects related to the treatment proposed). After that, the investigator advises the patient to take home the document, read it carefully and to identify doubts to be clarified in the next consultation. Thus, in the next visit, after the investigator explains and eliminates the patient doubts, it is known the patient's decision. When the patient decides to sign the informed consent, the investigator registers the information in clinical process and informs the SC, which is responsible to schedule, and ensure that all screening procedures are performed according to the protocol requirements.

- Screening**:** It is the process in which the investigator identifies the patients to a possible inclusion in a clinical trial (49). During my internship, I actively contributed to the schedule

of screening procedures. Firstly, I registered the patient in the IWRS or Interactive Voice Response System (IVRS) and I get the screening number of patient. This number is a crucial datum because it allows the patient identification on the study as well as the three initials of the first, second and third name. To access to this system I used the right credentials (an user identification and a password). Screening confirmations were sent via email or fax. Then, I scheduled all procedures required by protocol respecting the time window admitted by the same. The next step was to inform the patients about date and cautions before and after performing some exams.

During this phase, I had special concern to schedule the exams and, consequently, to ensure the exam's results, required to randomise the patient, within the timeline required per protocol.

After that, the investigator assessed the exams required to a possible randomisation (in another consultation) and checked the eligibility form with inclusion and exclusion criteria. If patient meet all criteria, the patient was randomised, if not the patient was considered as a screening-failure (SF). It both cases, the investigator register the data in clinical process of patient and contact the SC to randomise the patient. The UIC has a patient database that allows the unit staff to update and have access of data. When the patient decided to participate in a clinical trial, I added the data related to that patient to a recruitment list database. The patient status in this document was updated according to the status or participation of patient in the study (for example, if the patient was a SF, enrolled, discontinued the protocol, withdrew the informed consent, died).

- Randomization of Patients: It is the allocation method of patient population into groups that will receive different interventions which may be test or control groups (49, 54). This method assures that subject populations are similar in test and control groups, minimises systematic differences between groups that could affect the outcomes and provides a powerful basis for statistical inference (49, 54).

During my internship, I randomised several patients through the IVRS or IWRS. I had the opportunity to use both systems. I used the credentials to access to the platform. Then, I introduced all data by the system and at the end, the system assigned to the patient a medication number and, in some cases, a patient number (also called randomisation number). The system automatically provided real-time confirmation, via fax or email, the patient randomisation. After enrolling the patient, I contacted the investigator providing the

data about the patient randomised and study treatment, as applicable. This information was needed to complete the prescription form by investigator. Then, I wrote a letter (with patient identification and treatment assigned), and added the copy of therapeutics order sheet and the randomisation confirmation sheet to send (via fax) to the clinical trials pharmacy, where the treatment is prepared and dispensed. For example: if the treatment is oral, the operational assistants of UIC deliver the medication directly to the patient; if the treatment is intravenous, it is administered by study nurses in daily hospital.

IVRS/IWRS systems were programmed, not only to screening and randomisation, but also to register the SFs, obtain subsequent drug assignment or kit re-supply, discontinue a patient, acknowledge of study drug receipt, register an unscheduled visit, among others.

### 3.3.2 Clinic Visits

This phase of clinical trials comprised all activities related with patients, including scheduling, preparation and conduction of the visits.

- Schedule of Visits: From the moment that patient is randomised to the protocol, patients should comply with the procedures in accordance with periodicity required by protocol.

These procedures where scheduled by me. After confirming, through an internal electronic system of patient management named – “Oásis”, the dial and redial of blood tests (usually haematology, biochemistry and urinalysis) consultation and treatment cycle, I called the patients. During this call, the information communicated was the following:

- Date and time of blood tests, consultation and treatment cycle – usually, the blood tests and consultation were done in the same day, however, the treatment could be done in another day (according to the time window permitted per protocol) due to the prolonged treatment time and logistic;
- Remind the patient to bring the diaries and unused study medication, as well as packaging of used medication – concomitant medication (if applicable);
- Remind the patient to be fasted for biological sample collection;
- Other procedures: dial and/or redial of scintigraphy, computerised tomography and magnetic resonance).

In addition to my telephone contact, the administrative of the clinics of pathology sent a letter to the patient contemplating all procedures scheduled.

The management of patient's visits/cycles of the several clinical trials was difficult; however, the elaboration of a monthly calendar facilitates this task. This calendar was elaborated by all SC of UIC. In this calendar, each SC scheduled the patients visits included in its clinical trials. In more detail, I introduced the patient initials and the type of visit and/or the number of visit (for example, screening, cycle 1, end of treatment, follow-up, observational period) in the date that he/she had some procedure. Together with the identification of patient, it was identified the study, in which, the patient was participating. When, there was a change in calendar, I corrected and warned the trial staff that collaborates in the procedure.

- Preparation of the Visits: All clinical visits were previously prepared to guarantee compliance with all procedures established per protocol. Usually, I prepared the guide of visits some 2 or 3 days before the date of visit always in conformity with protocol. This guide contemplated a list with all topics needed to record in clinical process of patient by investigator. At the end of this guide, I provided the next date of study procedures (usually blood tests, consultation and treatment). Together with this guide I added the patient's clinical records, prescription form and other documents (computerised tomography request´s, some results of exams already performed).

- Patient Visits: In the patient's visit day, the preparation of visit (guide of visit and other documents) is attached to the clinical process that is sent to the clinic of pathology where the patient will be assisted. Before the visit, the patient goes to the local lab and the study nurse collects the central samples (these samples are stored, packaged and shipping to the central lab) and local blood samples (the parameters of these analysis are essential to evaluate the medical condition of patient before taking the treatment) required per protocol. During the visit the investigator perform a physical exam to the patient (and register the ECOG), lists the concomitant medication and evaluate signs, symptoms, AEs and blood tests parameters. If these parameters are compatible with the treatment (chemotherapy), it will be administered to the patient. When the blood tests parameters are changed but, according to the protocol the dose reducing is allowed, the patient will received the treatment but in a lower dose. If these parameters are not compatible with the treatment, it will be delayed and scheduled to another date. During the patient visits, the investigator contacted me and reported me the clinical status of patient. If the treatment was not delayed, I used the IVRS/IWRS system to assign the medication. Then, I contacted the investigator and provided the batch number, if applicable, that investigator wrote in the prescription form. After that, I wrote a letter (with patient clinical trial identification, treatment assigned and batch number, if applicable), and added the copy of

prescription form and the confirmation sheet of assigned medication to send (via fax) to the clinical trials pharmacy, where the treatment is prepared and dispensed. During the treatment, the study nurse of daily hospital is responsible to record the date in the patient's records (usually, included date and time of treatment administration, records of vital signs before, during and after the treatment, among others).

- Documents, CRFs, AEs and SAEs Report: After the visit, I reviewed all source documents (signed and dated) and new data generated. I also verified if the information required and contemplated in the visit guide, was completed in clinical processes by investigator as well as the records about the treatment administration filled by study nurses.

During my internship, I filled the eCRFs of many studies in which I introduced large amount of data. Thus, it was important to have the patient´s records completed with all required information because I needed to introduce the same in the eCRFs. When, any information was not totally clarified or there was missing data, I took notes in order to be explained or added by the investigator. Thus, information should be correctly recorded in all patient´s records to become the data entry, a more efficient activity.

I also had the opportunity to participate in the SAEs reporting. By GCP a SAE must be reported in 24 hours after the awareness of PI or sub investigator who fills a SAE from or enter the SAE data directly in the patient CRF (27). After the investigator fills the SAE form, I sent to the CRA and pharmacovigilance of the study within 24 hours after being detected. When I received queries related to the SAE report, I contacted the investigator in order to answer to the queries and clarify data. A report of the existing SAEs for a clinical trial is gathered, being transformed in Suspected Unexpected Serious Adverse Reactions that investigator have to be aware of.

- Packaging and Sending biological samples: When, per protocol, it was necessary to send a biological sample (solid tumours) of a patient to a country, I performed the following tasks:

  - Fill the sample request to the service of pathological anatomy;
  - Receive the sample from the service of pathological anatomy;
  - Organise the sample kit and package the sample according to the manual instructions;
  - Contact the carrier of the biological sample and register the reference number of sample.

During my internship, I participated in the packaging and sending of many biological samples of solid tumours. The processing, packaging and sending of blood samples were done by the study nurse. Additionally, when the tumour block was returned to the UIC, I delivered the biological sample to the service of pathologic anatomy with the minimum data required.

- Other activities performed after the visits: after the patient's visits, I performed some administrative, bureaucratic and data entry activities. Each SC acquires a patient clinical trial file, which contains information about exams, requisitions and results of the patient included in clinical trial. These files are archived in each SC room according to each pathology division. Thus, after the patient clinical visit, I archived the documents in that file in order to facilitate the data entry in eCRF.

According to the Law nº 46/2004, of August 19th (51), a patient that participates in a clinical trial has the right to be reimbursed for expenses performed during the participation on the same. The UIC has an internal regulation that sustains the way to protect the patient in order to be aware of the type of expenses that are paid. Thus, UIC achieves a transparent procedure way with the patient payment. For further understanding the procedures occur as following: the patient delivers the expenses;

- I checked these expenses according to the patient clinical visits and dates;
- I filled a specific expenses form where I reported all expenses and visits;
- I sent the expenses from to the financial assistant who is responsible for sending the information to the sponsor/CRO.

- Patient's Discontinuation: a patient may discontinue participation in a study due to the following reasons (49):

  - The patient withdrew the consent to participate in the study and intends to abandon the same;
  - Unacceptable toxicity resulting from drugs and/or study procedures;
  - Pregnancy;
  - Failure of a procedure and / or the study protocol, which prevents the final analysis of the patient;
  - Loss of contact with the patient;
  - Medical decision for safety reasons;
  - Interruption of the trial for safety or lack of efficacy reasons.

The last reason is one that most applies to the patient's discontinuation in oncology protocols. During my internship, I discontinued several patients due to the progressive disease. This reason is related to the interruption of trial due to the lack of efficacy of treatment. When, any exam or analytical parameter result demonstrate progressive disease, the investigator communicated immediately to patient their clinical trial exclusion. Subsequently, according to the protocol, I scheduled and prepared the end of trial visit. In this visit, the investigator registered the information related to the patient´s discontinuation in the clinical process. Through the IWRS/IVRS system, I discontinued the patients. The discontinuation confirmation sheet was sent via fax or email, and then, it was archived in the patient file. I also introduced the new data into the eCRF. In addition, the patient's discontinuation and related information was communicated to the sponsor/CRO and CRAs.

### 3.3.3 Monitoring Visits

During a monitoring visit the CRA oversees the progress of the clinical trial and ensures that it is conducted, recorded and reported according to the GCP and the applicable regulatory requirements (27). These visits are performed by qualified CRA's (properly trained and with specific scientific and clinical knowledge) appointed by the sponsor of each study. The purposes of monitoring visits are (27):

- Protection of rights and well-being of human subjects;
- Guarantee that reported trial data is accurate, complete and verifiable from source documents;
- Clinical trial compliance with protocol/amendments, GCP and regulatory requirements.
- During my internship I had the opportunity to participate in some monitoring visits.

Firstly, under the supervision of another SC delegated to the study, I scheduled the visit with CRA, usually by telephone or e-mail, in order to ensure the availability of SC and also the presence of the investigator(s) and other team members. Then, I recorded the date in an agenda and few days before the monitoring visit, I prepared and organised all essential materials to conduct the visit, for example, the patient files, the clinical processes of patients, the ISFs and other study dossiers and the CRF. Usually, CRAs sent by email the specific objectives of the visit in order to facilitate the preparation of necessary dossiers and documentation. Thus, I reviewed all documents to ensure the quality of the data and solve outstanding issues, related with queries, AEs and/or SAEs, missing data and unintelligible

data. I also checked and completed the eCRFs. If any data needed were missing in the clinical processes and/or patient files, I arranged a meeting with the investigator(s), in order to clarify the data (and if necessary, the PI performed an electronic amendment in the clinical process of patient). If any doubt or outstanding issue persisted, I appointed to solve with the CRA in the visit day. After organising the visit, the operational assistants stored the materials into the monitoring room until the day of visit.

During the visit, CRAs explored all documents and I accompanied their work and assisted them with my feedback and comprehension of source documents, clarifying issues and solving outstanding issues. When it was possible, all issues were solved in the visit day also with the collaboration of the investigator. However, there were other issues unable to solve in the day of monitoring visit. Hence, I took notes in order to solve them in the next visit scheduled. Few days after the visit, CRA sent a follow-up letter of the monitoring visit, including a description of the same and outstanding issues. This follow-up letter was very important to remember the outstanding issues and solve the same during the right time.

- Emergency Code Break: code breaking is defined as the breaking of the identification code of the blinded drug (49). I had the opportunity to follow the procedures concerning an emergency code breaking. Thus, after knowing the trial results by the sponsor/CRO, it was scheduled the patient´s visits. The patients were contacted and in the day of visit, the investigator explained the trial results to the patients. Then, according to the information provided to the investigator, the patient decided to continue or discontinue the trial.

## 3.4 Clinical Trial Closeout Activities

### 3.4.1 Closeout Visits

A closeout visit occurs after the last patient has completed all scheduled visits associated with the study. Throughout my internship, I did not participate in the tasks related associated to a closeout visit. However, I have some knowledge related to the purpose and preparation management of a closeout visit.

Firstly, to close out a study, the sponsor sent to the research team the end of study notification. In this visit, there are no more AEs and/or SAEs and queries clarification forms have been resolved, the database is locked and ready for statistical analysis, and the study conduct has ended. The whole concept behind a closeout visit is to ensure that everything is clarified and archived at the study site file and that the documentation is well organised and

will remain intact and be accessible in the future. A closeout visit of a trial can only be performed after the CRAs review both investigator/institution and sponsor files and confirmed that all required documents are in the adequate files (27).

### 3.4.2 Documents Archiving

According to the *Commission Directive 2005/28/EC of 8 April 2005*, the essential documents of the clinical trials should be retained for at least five years after its completion. However, the documents should be retained for longer periods by an agreement between the sponsor and the investigator (55). The essential documents should be archived to ensure that they are available, upon request, to the competent authorities (55). The medical files of subjects that participated in the study should be retained according to the national legislation for a period of time authorised by the institution (55). In this institution the maximum period of time permitted is 15 years (MS p.c.).

# 4. Discussion

The completion of my internship enabled me to reach a broader vision about the initiation, conduction and closeout of clinical trials in the oncology field. The clinical trials coordination was the focus of my activities, during which, I experienced difficulties, found challenges, developed strategies to combat adversities and, in the end, I acquired on the job experience.

As presented in the 1.1.2, the UIC was created in 2006 and today has a structured, organised and multidisciplinary team, whose members are segmented into well defined responsibilities. This fact became my first big challenge because I felt the need to integrate in the team and in the work circuit. The progressive knowledge about the structure and UIC procedures as well as the roles of UIC team members, specially the roles of a UIC SC's, facilitated my integration and learning process. I consider that this challenge was achieved because few months after the beginning of internship, I already felt and performed my activities as a team member of UIC.

According to the clinical R&D course, in European countries, where clinical research already reached high levels of maturity, the R&D of new medicines had a direct influence on the improvement of health and life quality of populations (4, 21). On the other hand, biopharmaceutical R&D also contributed to the wealth creation, through the employability and to the improvement of Europe´s trade balance (4, 21). The globalisation and the economic and social development are creating big challenges to the health sector and, more specifically, for the pharmaceutical industry (4). During the R&D of new medicines, the clinical trials are the major portion of the investment (29). This has been leading the pharmaceutical industry to search for places where the clinical trials completion may be more efficient (23). The reallocation of clinical trials to the developing countries reflects a loss of efficiency and, consequently, lower attractiveness of developed countries for clinical trial completion (4, 23). In Portugal, the unfavourable regulatory framework (excessively bureaucratic) has been determining this reallocation (4). Thus, the clinical trials are the research paradigm of new medicines (4). The clinical research in Portugal has been losing its leading position within the overall investment in health (4). I consider this trend incomprehensible because my experience enabled me to contact with distinct clinical research professionals and understand that Portugal has capable professionals and also a good scientific capacity in research and health institutions. I realised that the UIC of IPOP is an exception to the negative trend in Portugal, because the number of authorised clinical trials and the patient's recruitment rate has been increasing (4). Once again, my experience

enabled to understand and conclude that the key to the success of the UIC of IPOP is related to the confidence, motivation, interest and devotion of a multidisciplinary team, including the PIs, sub-investigators, manager of GCP and quality, operational manager, SCs among others elements and in addition, the continued commitment of IPOP AB.

My internship involved generic and specific training components. Therefore, at the beginning of my internship, I completed online training courses in ICH/GCP and in Electronic Data Capture systems. The first training was essential to conduct all my activities as SC. During the Degree and Master´s Course I learned that the understanding and compliance with GCP is the key to the success to perform clinical research, assuring that the rights, safety and well-being of trial subjects are protected (27). The second training was imperative to perform the data entry task and also to introduce large amount of data in the eCRFs of several clinical trials protocols. The platform of Electronic Data Capture system may vary according to the clinical trial, so I felt the need to perform the online training courses in three different platforms (referred 1.2). These online courses introduced me to the specific platform and ensure that I was able to perform the data entry task. I also consider that the understanding about the characteristics, symbology and management of each platform enabled to improve my performance in data entry in eCRF. On the other hand, I also felt the need to deepen my understanding about concepts and classification systems found in the oncology clinical trials protocols that are daily used by healthcare professionals in medical records and exams of clinical trials subjects. I designated them as support tools. My acquaintance with these tools enabled me to better understand the contents of medical records and exams, use and apply them in an accurate manner (for example, in the tasks performed before, during and after the patient clinic visits).

During my specific training of internship, I had the opportunity to participate in 6 phase II and 25 phase III clinical trials of different clinics of pathology. I recognise that this opportunity was very important because I acquired a greater knowledge and experience in oncology protocols of different therapeutic indications (including solid and liquid tumours). The clinical trials indicated to test new treatments (or new treatment combinations) for liquid tumours required a larger amount of procedures as well as a large complexity of the same. Thus, I consider the Onco-Haematology as the clinic of pathology with the more complex clinical trials protocols according to my experience as SC.

Considering the clinical trials coordination activities - initiation, conduction and closeout – I did not provide a similar contribution in the three steps. I participated intensively in the clinical

trial conduction activities. My disproportionate contribution to the steps referred above was due to the fact that UIC team members have already well defined roles, functions. In addition, some tasks (for example the tasks that occur until the clinical trial approval) are confined to other UIC professionals (operational manager and manager of GCP and quality). Nevertheless, I deepened and consolidated theoretical knowledge in tasks that I did not execute because I had an oral session in which it was explained the content and the order in which they happen.

With respect to the clinical trial conduction activities, I accomplished and performed them according to distinct oncology protocols for several oncology diseases, including different study designs and procedures. I acquired a greater knowledge about cancer disease, including diagnostic and assessment methods and therapeutics associated.

During my internship, I had the opportunity to participate in a clinical trial initiation activity that was useful because it enabled to get a deep understanding about the clinical trial procedures as well as some particularities related to the study. On the other hand, the background acquired during this visit facilitated the work of the SC in supporting the research team members.

The conduction of a clinical trial was very challenging. For each clinical trial, there was a research team constituted by professionals with a different way of working and organisation. Therefore, I needed to adapt, work together and meet the expectations of different professionals, including investigators and CRAs. I realised that each investigator had its own way of working and when new situations and doubts appeared they must be solved quickly and safely. Each screening, randomisation or clinical visit were carefully scheduled and prepared ensuring that timings and procedures were compliant with protocol. I felt the need to establish good communication flows between not only investigators but also study nurses (responsible for blood sample collection and treatment administration), assuring the acquaintance of them with procedures, its completion and execution according to the protocol. The organisation and planning of conduction activities was a good work methodology because this enabled to distinguish the tasks according to the priority. Also, the data collection and verification (after clinic visits, for example) was useful because all patient data must be recorded, since, what is not recorded, does not exist. Then, the organisation of source data in respective dossiers ensured to protect and maintain updated data. This task was very useful because when I needed to introduce the data into eCRF, I already had the necessary clinical patient records archived into the dossiers. Thus, I could follow in detail the

clinical condition of patients and, at the same time, the work was prepared to support the periodic monitoring visits. This task tested my ability to communicate and opinion share. My support in the periodic monitoring visits and the contact with CRAs helped me to overcome some fears. The interaction, exchange of experience and training with CRA strengthened the work between two different professionals of clinical research. Consequently, the results of this cooperation were reflected in an improvement of work efficiency. I acquainted myself with CRA functions and roles and understood that a good work preparation to these visits will be preponderant to assist the both functions. Thus, my contribution in monitoring visits was very important to adjust and improve my performance as SC.

In order to conclude my challenges and positive marks experienced during my internship, it is important to emphasise that the experience as SC enabled me, each day, to face and solve new cases and situations. This was very positive for me because I learned to prioritise and act when the adversities arise and, consequently, improved my technical and interpersonal skills and gained experience as SC trainee. I also felt motivated and enthusiastic to conduct the activities as SC trainee during the 8 months of experience.

On the other hand, I also point some negative aspects that are necessary to improve in the future. The first is that, I did not establish a personal contact with the patient other than the phone contact. I regard this fact as limiting because the oral communication is a more efficient method to know the patient expectations, doubts, fears, as well as family support, professional situation and socio-economic conditions. The knowledge of these circumstances is essential to protect and safeguard the rights of patient. A referred above, my contribution was not in equal terms to the three clinical trial coordination activities. I did not gather know-how in the initiation and closeout activities and I only have the theoretical knowledge about them. The initiation activities are very important to acquaint me about the tasks circuit and interactions with regulatory authorities until the clinical trial approval. During the trainee, I did not collaborate in any audit regarded as an opportunity of learning and be aware about what the research team should or not do in a clinical trial, quality of team's work, compliance with protocol and legislation and future advice to pursue. An audit is a chance to recognise and improve the trial site performance. In addition, during these 8 months, I did not have the opportunity to collaborate in observational studies and so to experience, in practice, the differences between clinical trials and observational studies.

In addition to the positive and negative marks presented, I experienced difficulties and developed strategies to combat them. My first difficulty was to understand and integrate

myself in the UIC multidisciplinary team. In order to overcome this difficulty, I tried to understand and acquaint about the roles and functions of each UIC team member. Then, I developed the work according my roles and responsibilities and assisted the clinical research team in clinical trial activities. At the end, I communicated sharing my feedback to the UIC team members, mainly to the SCs and Operational Manager. Another difficulty was to understand the role and the work (activities, tasks and procedures) of a SC in the UIC. This topic includes the manner as a SC in UIC schedules, prepares and conducts a patient clinic visit; the patient's circuit in the IPOP, during a clinic visit; the communication´s flow and interaction between the different research team members (study nurses and investigators, for example). The strategy to combat this problem was to put into practice the SC tasks and focus on the tasks that for me were more complex to execute. The tasks more difficult included my ability to communicate, namely, the ability to transmit ideas and opinion share showing the critical spirit with different healthcare professionals. The third difficulty was dealing with unexpected situations, involving patients, failure of electronic systems, changes in deadlines, among others. These adversities were faced as a challenge. Thus, I needed to understand what to do in order to solve the problem, including: the perception about what UIC team members and other professionals were able to assist me, as well as the awareness about how to act depending on each situation. This strategy enabled me to develop and practice the ability to problem's solving and establish the priorities according to the situation.

According to my primary and secondary objectives defined in the section 1.2, I have several points to criticize.

In this way, I gathered personal and professional experience, skills and competences including:

- Experience as clinical trials SC in oncology protocols;
- Knowledge about protocols for different oncology therapeutic indications, specially the protocols of Digestive clinic of pathology;
- Working tools and methodologies with the experienced work team members: these tools facilitated my integration in the work operations;
- Cooperation with a multidisciplinary team work me to perform, develop and specialise in the oncology clinical studies and prepares me to integrate the labour market;
- Demonstration the ability to achieve the proposed activities in an effectively and efficiently manner, fulfilling the deadlines established;

- Ability to time management according to the priorities established;
- Improvement of the critical thinking analysis;
- Development of positive interpersonal relationships among team members of UIC, healthcare professionals and other professionals included in the study team;
- Demonstration of the problem-solving ability. I developed the ability to communicate with clinical research professionals which facilitated my adaptation to the clinical trials coordination activities.
- Improvement the ability to communicate;
- Professional and personal growth;

On the other hand, during my internship, I also would like to develop the following competences:

- Experience in all clinical studies coordination activities, in order to become my experience as SC complete;
- Autonomy to perform the type of activities associated with clinical trials and observational studies conduction: I did not have the experience in observational studies conduction, however, I would like to acquired experience and know-how in these studies;
- Knowledge and training in the preparation, conduction and reporting of an audit in the context of a clinical study: this is an activity inherent to the clinical research, which I did not have the opportunity to collaborate. However, since the beginning of my internship I was trained to conduct all my activities in the terms of an audit;

In sum, the knowledge gathered during the Degree in Biomedical Sciences and Master's Course in Pharmaceutical Medicine was deepened and applied as well as it was enriching and motivating to transpose the theoretical knowledge to the practice of clinical research. I recognise that the basis acquired during the Master's Course were very useful to have a better understanding and performance in clinical trial coordination activities. In addition, all that I learned during my Degree and Master´s Course became clearer. Thus, in general, I consider that, inside of the clinical research area, I achieved this knowledge in the field related to the clinical trials. Additionally, I wish that in the future, the key stakeholders will join forces to promote and strengthen the clinical research in Portugal, specially, in the oncology field.

# 5. Conclusions

This 8-month internship as SC in the UIC of IPOP provided me skills and expertise essentials to the coordination of clinical trials in the oncology field. I recognise that I would never acquire these skills and competences, if I had not gone through this experience.

During my internship, I acquired the theoretical basis about how to initiate, conduct and closeout a clinical trial in UIC of IPOP. I participated intensively in clinical trial coordination conduction activities of several clinics of pathology including Urology, Gynaecology, Digestive, Lung, Soft Tissue and Skin, Head and Neck, Onco-Haematology, Breast and Paediatry. On the other hand, the experience in the UIC was even more challenging because, at the some point of my internship, I acquired more responsibility and autonomy to coordinate the clinical trials of the Digestive pathology. This responsibility was not easy and I needed to work a lot and overcome some adversities but today I recognise that this challenge became an opportunity. Currently, I coordinate the clinical trials of the Digestive clinic of pathology. Thus, at this level, I had the opportunity to gain know-how, experience and expertise in oncology clinical studies conduction activities as well as I know and understand the procedures associated to the operation of UIC, as a clinical research centre.

The background acquired during the Degree and the first year of Master´s Course in Pharmaceutical Medicine influenced, positively, my performance evolution throughout the internship as SC. This background was applied, consolidated and enabled to enrich my practice associated to the clinical trials. On the other hand, my experience as SC in the UIC enabled to improve my interpersonal skills. I felt that I became in a more proactive and assertive member, I improved the ability to communicate, transmit and share ideas, opinions and also I developed the critical spirit together with the multidisciplinary research team members.

My internship completion enabled me to feel able to initiate a career as a clinical research professional, specially a SC. Under this job, I hope to bridge the gaps of my training. Thus, I hope to have the opportunity to collaborate, in a similar way, in all clinical trials coordination activities and specialise me as SC.

Thus, after concluding my training, I feel motivated to develop a career the in the clinical research area. In the near future, I hope to have the opportunity to contribute to the

observational studies. I also wish that pharmaceutical R&D trends will be reversed, promoting and strengthening the clinical research in Portugal namely in the oncology field.

Due to all the reasons presented and discussed, I classify my experience as challenging, interesting, motivating and enriching but not complete. Thus, in the near future, I hope to gather more and new experience in clinical research area and grow as professional of clinical research.

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