Universidade de Aveiro
2014

Secção Autónoma de Ciências da Saúde

Ana Luísa Oliveira de Simas

Relatório de estágio: Coordenação de Ensaios Clínicos em Oncologia

Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2014

ANA LUÍSA OLIVEIRA DE SIMAS

RELATÓRIO DE ESTÁGIO: COORDENAÇÃO DE ENSAIOS CLÍNICOS EM ONCOLOGIA

TRAINING REPORT: CLINICAL STUDIES COORDINATION IN ONCOLOGY

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Dr.ª Juliana Maria Salsa Ferreira, Gestora Operacional e Coordenadora de Estudos da Unidade de Investigação Clínica do Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. e da Professora Doutora Maria Joana da Costa Gomes da Silva, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

Training report presented to the University of Aveiro to fulfil the necessary requirements to obtain a Masters' Degree in Pharmaceutical Medicine, held under the scientific guidance of Juliana Maria Salsa Ferreira, Operational Manager and Study Coordinator of the Portuguese Institute of Oncology Porto, and Maria Joana da Costa Gomes da Silva, Professor of the Health Sciences Department of the University of Aveiro.

Dedico este trabalho aos meus Pais, e à memória do meu Avô José.

o júri

presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático, Universidade de Aveiro
vogal – arguente	Professora Doutora Alexandra Isabel Cardador de Queirós Professora Coordenadora sem Agregação, Universidade de Aveiro
vogal – orientadora	Prof. Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta, Universidade de Aveiro

agradecimentos

À Universidade de Aveiro e ao Professor Luís Almeida, Diretor do Mestrado em Biomedicina Farmacêutica, por terem apostado nesta formação. Ao Professor Bruno Gago, por toda a disponibilidade e dedicação à Licenciatura e Mestrado, e pela ajuda na procura de estágio.

Ao Dr. Laranja Pontes, Presidente do Conselho de Administração do IPO-Porto, e ao Dr. José Dinis, Responsável da UIC, pela oportunidade de estágio nesta equipa.

À Dra. Juliana Ferreira, orientadora do meu estágio curricular no IPO-Porto, por me ter acolhido, por todo o carinho, amizade e compreensão, pela partilha de conhecimentos e experiências e, pela revisão deste relatório.

À Dra. Joana Silva, orientadora do meu estágio na UA, por toda a orientação, pelas ideias e estratégias desenvolvidas, pela disponibilidade e dedicação à revisão deste relatório. A sua intervenção foi imprescindível.

À Dra. Joana Maia, pela amabilidade, partilha de conhecimento e revisão informal deste relatório.

À Dra. Manuela Seixas, pela orientação inicial do meu estágio, carinho com que me recebeu, e confiança que depositou em mim.

À Inês Carvalho, pelo carinho, e também pelo exemplo. À Inês Soldin, pelo acolhimento na cidade do Porto e pela amizade em crescimento. À Márcia Correia, por ser o meu apoio e um grande exemplo, por ser tão especial, pela amizade infinita.

À Maria João Figueiredo. À Mara Rodrigues, Patrícia Rodrigues e Jorge Ribeiro. À Filipa Rocha. À D. Maria da Luz pelo carinho.

À Inês Maia e Sandra Alves, por estarem sempre presentes (em especial nesta fase, obrigada), e pela amizade incondicional, assim como à Margarida Oliveira, Rita Fonseca e Cláudia Nunes.

Ao Pedro Batista, Pedro Jorge, e Paula Moreira, pelo acompanhamento no meu percurso académico, pela partilha e amizade.

À Joana Seara e Guilherme Luz, por serem um orgulho, pelo carinho.

À Júlia Silveira, por me ter acolhido em Lisboa durante o Mestrado, e pela amizade de há cerca de duas décadas.

À Bárbara Almeida, pela partilha e amizade durante o período de estágio.

Aos meus Pais Lucília e Jorge, por serem um exemplo de amor e união, por me inspirarem, por me incentivarem a crescer e atingir os meus objetivos, por serem o meu porto seguro, por todo o apoio, por me terem possibilitado a oportunidade de ter formação superior, e por me fazerem sentir amada todos os dias. Ao meu irmão Miguel, pela confiança que tem em mim, pelo apoio e amor.

À minha Madrinha Celestina Oliveira, por ser a minha mentora desde longa data, por ter sempre um conselho acertado, pela sua amizade inestimável. À minha tia Aurinda Oliveira, pelo seu grande coração.

À minha Avó Neli, pelo amor incondicional. À minha Avó Helena pela amizade, e ao meu Avô João, pelo orgulho que tem em mim.

A toda a minha Família.

palavras-chave

Coordenação de Ensaios Clínicos, Ensaios Clínicos, Medicina Farmacêutica, Investigação Clínica, UIC, IPO-Porto, Oncologia, Pulmão, Urologia, Ginecologia, Pediatria, Cuidados Intensivos.

resumo

Este relatório descreve o estágio curricular em Coordenação de Ensaios Clínicos na Unidade de Investigação Clínica do Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E., no âmbito do Mestrado em Biomedicina Farmacêutica na Universidade de Aveiro.

Este relatório começa por descrever o Estado de Arte no Processo de Investigação & Desenvolvimento Farmacêutico, em especial na Oncologia, na Europa. São também enfatizadas tendências atuais nesta área e destacadas as especificidades das populações especiais e vulneráveis, relevantes no contexto da Investigação Clínica em Oncologia, e enquadradas no âmbito deste estágio.

As atividades de coordenação de ensaios clínicos foram essencialmente realizadas nas Clínicas de Patologia do Pulmão, Urologia, Ginecologia, Pediatria, e no Serviço de Cuidados Intensivos. As atividades desenvolvidas tinham como objetivo principal adquirir experiência em ensaios clínicos oncológicos, e reforçar os conhecimentos adquiridos na minha formação académica. Estas atividades incluíram triagem e aleatorização de doentes, preparação e processamento de visitas de estudo, entrada de dados e resolução de questões, e gestão de documentos, entre outras atividades transversais aos 15 ensaios clínicos acompanhados.

Globalmente, o estágio traduziu-se numa boa percepção das atividades envolvidas na realização de ensaios clínicos num hospital, e numa exposição valiosa ao mercado de trabalho. Também fortaleceu o conhecimento adquirido na minha formação académica. O estágio permitiu desenvolver competências e aptidões tanto no nível profissional como pessoal, tais como lidar com situações inesperadas, e desenvolver estratégias para ultrapassar desafios. Aprofundei a minha visão de profissões em investigação clínica, e espero continuar a enfrentar e transpor novos desafios nesta área.

keywords

Study Coordination, Clinical Trials, Pharmaceutical Medicine, Clinical Research, UIC, IPO-Porto, Oncology, Lung, Urology, Gynaecology, Pediatrics, Intensive Care.

abstract

This report describes a curricular training experience in Study Coordination, developed at Unidade de Investigação Clínica (Clinical Research Unit) of Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. (Portuguese Oncology Institute-Porto), in the ambit of the Master in Pharmaceutical Medicine at University of Aveiro.

This report describes the State of the Art in Pharmaceutical R&D Process in Europe, especially in Oncology, emphasising its current trends and stressing specificities of special and vulnerable populations, in the scope of the traineeship.

The study coordination activities were essentially performed in the Pathology Clinics of Lung, Urology, Gynaecology, Paediatrics, and the Intensive Care Service. The activities developed had the main goal of acquiring experience in oncology clinical trials, while reinforcing the knowledge from my academic background. These activities included screening and randomisation of patients, preparation and processing of study visits, data entry and query resolution, and documents management, among other activities transversal to the 15 clinical trials, accompanied in the traineeship.

Globally, the traineeship allowed a good overview of the activities involved in the conduction of clinical trials in a hospital, and a worthy introduction to the marketplace. I strengthened the knowledge acquired from my academic background. I developed competences and skills at the professional and personal level, such as dealing with unforeseen situations, and developed strategies to overcome challenges. I sharpened my vision of careers in clinical research, and hope to continue addressing new challenges in this area.

Table of Contents

List of figures

List of tables

Abbreviations

AE	Adverse Event
CEIC	Comissão de Ética para a Investigação Clínica
CI-IPOP	Centro de Investigação do IPO-Porto
CNPD	Comissão Nacional de Protecção de Dados
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Clinical Trial
CTA	Clinical Trial Assistant
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic Case Report Form
EMA	European Medicines Agency
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IMI2	Innovative Medicines Initiative 2
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde I.P
IPO-Porto	Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E.
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
PHR	Personal Health Record
PI	Principal Investigator
R&D	Research and Development
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SC	Study Coordinator
TNM	Tumour, Node, and Metastasis
UIC	Unidade de Investigação Clínica

1. Introduction

This report presents an overview of the activities performed as trainee in Clinical Studies Coordination, from September 2013 to May 2014. The traineeship took place at the Unidade de Investigação Clínica (Clinical Research Unit – UIC) of Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. (Portuguese Oncology Institute – IPO-Porto). This curricular training is included in the Master of Science in Pharmaceutical Medicine of the University of Aveiro, which is affiliated to the PharmaTrain programme (1).

This report characterises the UIC regarding its structure and organisation, as well as its patients' recruitment potential for Clinical Trial (CT), and presents the objectives for this training at IPO-Porto. Following, it describes the State of the Art in Clinical Research and Development (R&D) in Europe and specifically the trends in Clinical Oncology Research. The activities developed during the traineeship are described in the Generic and Specific Training sections, the first regarding activities that contributed for the enforcement of my activities, namely regarding oncology CTs, and the later referring specifically to the CT coordination activities. This report is completed with a Discussion of the outcomes of this training period, regarding the main features of this experience, and a Conclusion.

1.1. HOST INSTITUTION – UIC AT IPO-PORTO

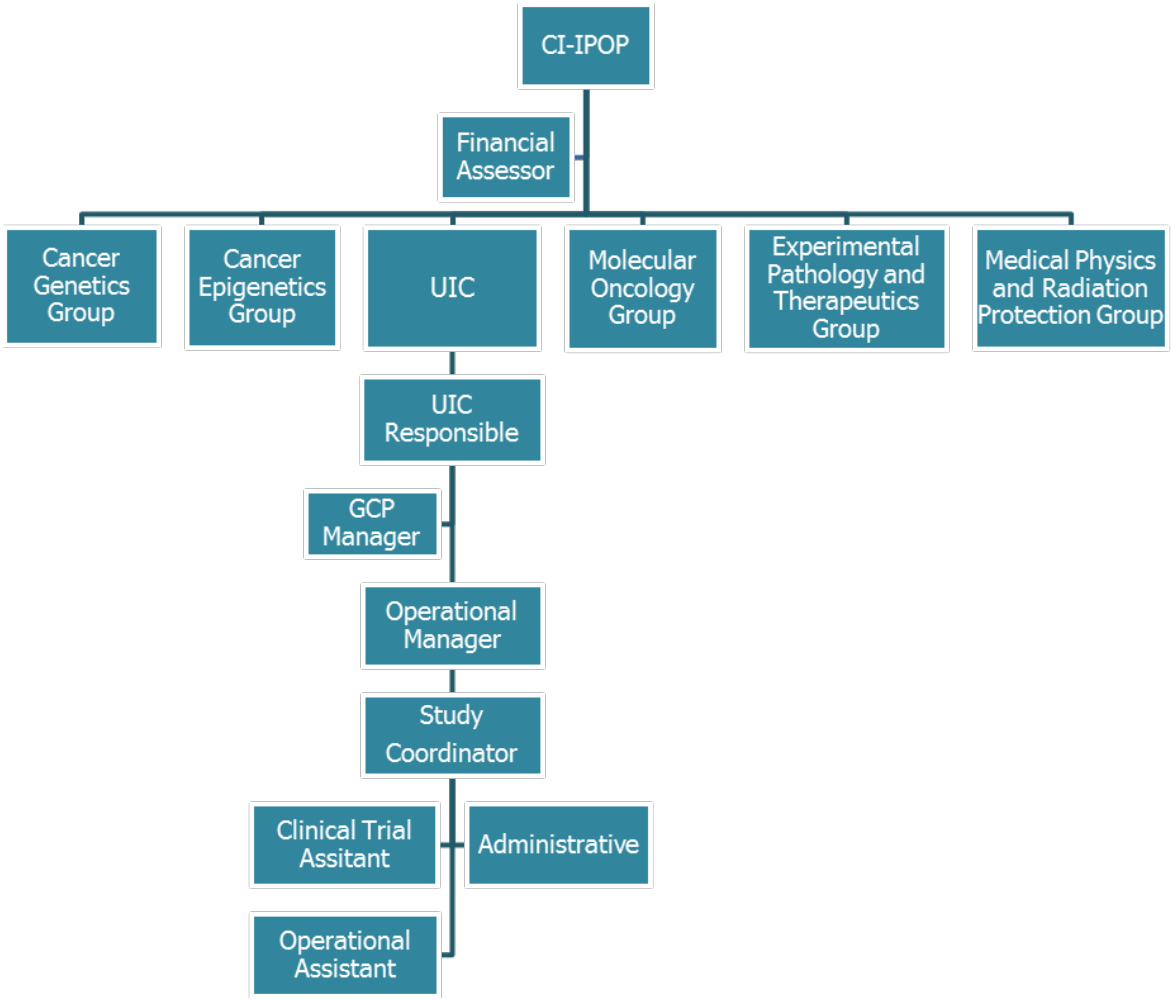
IPO-Porto is a specialised Portuguese cancer hospital institution, whose mission is to provide patient-oriented healthcare in time, without setting aside the prevention, investigation, training and, education in oncology, while ensuring high quality, humanism and efficiency levels (2). Professor Francisco Gentil was the major Sponsor of the first Portuguese cancer institution, created in 1923 in Lisbon. After that, another centre was created in Coimbra and, in 1974, IPO-Porto was created (3).

During the traineeship, in April 17th of 2014, IPO-Porto has completed its 40th anniversary and to mark the occasion, the institution was temporarily named "Instituto Português de Oncologia e Esperança do Porto", which stands for "Portuguese Institute of Oncology and Hope", emphasising what the institute aims to mean to the patients (4).

Within IPO-Porto, the UIC was created in 2006 (5) as part of the structure of the "Centro de Investigação do IPO-Porto" (IPO-Porto Research Centre – CI-IPOP), which was formally recognized by the Portuguese "Science and Technology Foundation" as a R&D unit in 2004 (6). CI-IPOP is a research centre for the comprehension of cancer's

pathobiology mechanisms, aiming to achieve and facilitate the prevention, early diagnostics, prognostic assessment and, development of more effective therapies (7). CI-IPOP is presently directed by Manuel Teixeira, MD, PhD and is organised in the UIC and 5 Research Groups: Cancer Genetics, Cancer Epigenetics, Molecular Oncology, Experimental Pathology and Therapeutics, Medical Physics and Radiation Protection; (as shown in Figure 1) (7).

Figure 1. Organogram of UIC within CI-IPOP [adapted from(8)]



The mission of UIC is to support the conduction of CTs with investigational medicinal products (IMP), such as experimental medicines or medical devices, as well as non-interventional studies (5). The UIC is coordinated by José Dinis, MD (6, 7), since 2006. Its goals are to attract the best worldwide CTs to the IPO-Porto, support CTs conduction and ensure protocol and procedures compliance (5, 9).

Regarding most pathologies treated at IPO-Porto, this institution is considered a reference centre for CTs (5, 9). The UIC showed a sustained increase of the CT's number and the number of patients recruited, while reducing CTs' implementation time, which increases its competitiveness and improves UIC's performance (5). UIC supports CTs promoted by the pharmaceutical industry, by collaborative groups, by Investigator initiative and by the European Organization for Research and Treatment of Cancer (8-10). It is also the aim of the UIC to create a Phase I Unit in the short term (5, 10).

1.1.1. Structure and Organisation

The main action centre of a CT is the study site. The CT procedures are conducted at the study site, where data is generated, collected and reported, complying with the CT protocol. Ultimately, data gathered at all centres determine the outcome of an IMP (11). To comply with every CT requirements, it is crucial to have a dedicated team working at the research centre.

UIC has a team that supports the participation of most clinical departments of IPO-Porto in clinical trials. Those departments assign an Investigation Team to a given CT, as they are responsible for allocating the Principal Investigator (PI), Co-Investigators and Study Nurses to the CT (8).

At IPO-Porto, the Investigational Team must have at least one PI, two Co-Investigators, two Study Nurses from the Pathology Clinic where the CT is conducted, two Study Nurses from the Hospital de Dia (Day Care Hospital), if applicable, two Pharmacists, and two Study Coordinators (SCs) (8). UIC has to ensure that the CT's team is properly defined (8).

UIC supports the Investigational Team, and regulatory affairs of the CTs (8). Therefore, UIC is a structured and specialised team, working exclusively with Clinical Studies. The Organogram of UIC is presented in Figure 1. The functions of each member of the UIC and Investigational Team members are described on the UIC's Internal Regulation, as well as Standard Operating Procedures regarding the regulatory affairs (8).

Since the beginning of my traineeship, some of the staff functions have been re-assigned, due to the reformulation of the team. When I started the traineeship, the Operational Manager was responsible for that function only. On December 2013, the person responsible for Operational Management resigned from IPO-Porto. To fulfil that role, two of the existing SCs accumulated the Operational Manager's role since the

beginning of 2014: Inês Carvalho, MSc and Juliana Ferreira, BSc. Each Operational Manager divides her attention by different Pathology Clinics. Subsequently, this triggered an increased workload for both Operational Managers. To overcome that difficulty, some of the Operational Manager's functions were reassigned to the Good Clinical Practice and Quality Manager (12, 13). Furthermore, a new role—Clinical Trial Assistant (CTA)—had already been created in September 2013, to assist the SCs on their tasks. Some of the administrative functions were also allocated to the CTA's role. The teams' members and their respective updated roles are described below (8):

- **Investigational Team**

Principal Investigator: Evaluates the proposed CT and financial protocol; defines the CT's team; cooperates in the CT's submission and approval process; complies with the protocol and regulations; informs and obtains patient's Informed Consent; records and notifies Adverse Events (AE); keeps the patients' Personal Health Records (PHRs) up to date; and ensures confidentiality and medical assistance to the participants.

Co-Investigator: Has the same role as the PI, regarding the aspects related to the CT conduction. Also, the Co-Investigator has to inform the PI/SC if there is a non-compliance situation.

Study Nurse: Performs every nursing CT procedures defined in the protocol, such as: evaluate and record clinical data; prepare and administrate IMPs; explain its instructions to the participant; drug accountability; inform the Investigator of non-compliance situations; collect, process and send biological samples according to protocol; and verify questionnaires completion.

- **Pharmaceutical Services**

Pharmacists: Performs every pharmaceutical procedures defined in the protocol (8).

- **CI-IPOP**

Financial Assessor: Evaluates, reviews and emits a Financial Opinion regarding the CTs' Financial Protocols; prepares the distribution proposal of the financial compensations; and complies with the procedures for compensation of CT participants' expenses, in accordance with the protocol.

Financial Assistant: Assists the Financial Assessor on his/her activities.

- **UIC**

UIC Responsible: Represents IPO-Porto externally and technically assists the Administration Board on CTs matters; ensures the communication with the several departments and services of IPO-Porto involved in CTs; evaluates the operational and scientific feasibility of CTs; approves the financial proposals; evaluates the educational needs of the team's elements and their performance.

Good Clinical Practice and Quality Manager: Proposes, develops and maintains the Good Clinical Practice (GCP) System; performs Internal Audits and participates in the support team to the external audits and inspections; maintains the records of the quality documents necessary to CTs conduction, in coordination with the several departments and services of IPO-Porto; prepares, submits and accompany the "Dossier of Approval Request for the conduct of a CT at IPO-Porto"; receives and fast-forwards the "Feasibility Questionnaires" of new CTs, and maintains its record and their respective response times; reviews the records of CTs procedures done to each participant and informs the Financial Assessor, to allow the billing to the Sponsor.

Operational Manager: Manages UIC's daily activities and coordinates the activities of each UIC member; prepares and participates on the team of support to internal and external audits and inspections; participates in the evaluation of the employees performance; coordinates, with entities external to IPO-Porto, the conduct of complementary diagnostic exams required by the CT protocols; manages reclamations and conflicts, CT protocols deviations, and notifies the Sponsor.

Study Coordinator: Implements CTs, supporting the CT team in all activities related with the preparation and organization of the procedures and documentation; schedules and gives support to the monitoring visits; participates in Investigators meetings; participates in site initiation visits; ensures that the CT team complies with the GCP and with the CT protocol; informs the Operational Manager of the protocol deviations; reviews the PHRs, ensures that the information necessary to fill the Case Report Forms (CRFs) is complete and up-to-date and, completes the CRFs accordingly and on time; supports the investigators in queries resolution and in reporting Serious Adverse Events (SAE) to the Sponsor; maintains the CT procedures registry updated; complies with the procedure respective to the compensation of CT participants' expenses, according to the protocol; updates the information about each CT status, reporting the CT status internally and to the Sponsor.

Clinical Trial Assistant: Assists the SC on his/her activities, namely the archive of documents and its update, and scheduling the participants' visits and exams (and verifying the agenda); process the participants' expenses and prepare its reimbursement; maintains the essential CT documentation up-to-date and archived, complying with the Sponsor procedures; participates in site initiation visits; supports the completion of Quality of Life Questionnaires by the participant; and receives any external elements to the IPO-Porto.

Administrative: Supports the UIC on every activity related with CTs, namely the preparation and internal distribution of CTs documentation and material; receives and distributes every correspondence and CTs materials in the UIC, and dispatches necessary material to the exterior.

Operational Assistant: Controls and ensures the availability of the material necessary to the UIC functioning; manages the PHRs of the participants; distributes and collects CTs' material as needed within IPO-Porto; distributes mailing; and articulates the distribution of the Monitoring Offices with the SCs, according to the monitoring visits agenda and prepares them for each visit with the adequate material.

At UIC, there is one UIC Responsible, one GCP and Quality Manager, two Operational Managers, five SCs, three CTAs (one of them also accumulating administrative functions), and two Operational Assistants. Each SC has a Pathology Clinic assigned (8). The Pathology Clinics that have a specific SC associated are: Urology; Gynaecology; Lung; Paediatrics; Soft Tissue and Skin; Endocrine Tumour; Head and Neck; Breast; Onco-Haematology; and Digestive. The Services with an assigned SC are: the Intensive Care Service; and the Bone Marrow Transplantation Service.

The Soft Tissue and Skin, Head and Neck, Endocrine Tumour, and Breast Clinics are assigned to one SC. The Onco-Haematology Clinic and Bone Marrow Transplantation Service are associated to a SC. Given the workload of the aforementioned clinics, some of the CTs of the Breast and Onco-Haematology Clinics are the responsibility of another SC, whom accumulates CTs of both clinics. The Digestive Clinic is associated to another SC. The Clinics of Urology, Gynaecology, Lung, Paediatrics, and Intensive Care Service are assigned to another SC, whom I accompanied.

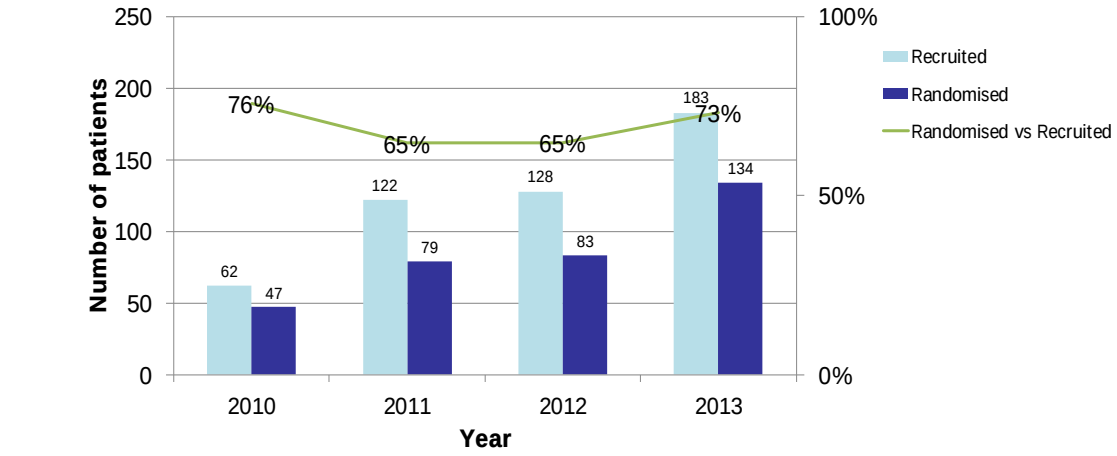
Given the confidentiality issues associated with the conduction of CTs, UIC's facilities are of controlled access (8, 9). Only the UIC members have permanent access to the facilities. Members of the CTs teams have temporary access to UIC's facilities, as well as external elements to IPO, such as Clinical Research Associates (CRAs) or auditors. A

plant of the UIC's facilities can be encountered in the UIC's internal regulation (8) and also in (14), in page 5.

1.1.2. Recruitment at IPO-Porto

UIC has shown a sustained growth of the recruitment rate in the last years (9), as shown in Figure 2.

Figure 2. Recruitment Rate at IPO-Porto from 2010 to 2013 [adapted from (15)]



In 2010, 76% of the recruited patients were randomised (Figure 2). This means that 25% of the patients recruited (Figure 2) were screening failures. In 2011 and 2012, the recruitment increased steadily. However, 65% of the patients were randomised, which means a higher screening failure rate, despite the efforts to include more patients in CTs. It is important to clarify that the number of screening failures does not depend on the centre, since many patients enter CTs, perform the exams necessary to confirm eligibility but the exams' results do not comply with the selection criteria and, therefore, are not randomised.

If we look alone at the number of randomised patients since 2010, it has increased. The percentage of patients randomised versus patients recruited, in 2013, increased to 73%, which translates the effort of randomising patients at IPO-Porto, by increasing the recruitment numbers (Figure 2).

Thus, IPO-Porto has great potential of increasing its recruitment and number of patients participating actively in a CT.

1.2. OBJECTIVES

This section presents my objectives at UIC, as a trainee. The primary objectives represent the aspects I considered necessary to achieve a proper training and consider myself a professional of clinical research. The secondary objectives represent specific aspects I would like to develop or acknowledge, in the context of an investigation centre.

1.2.1. Primary Objectives

The main objectives were to:

- develop skills and gain experience in Study Coordination;
- reinforce and apply the knowledge acquired in the BSc and MSc;
- have a perspective of the working environment;
- understand the functioning of a clinical research centre.

1.2.2. Secondary Objectives

The secondary objectives were to:

- perform the daily activities of a SC on-the-job and in time;
- understand the communications' flow in a clinical research centre;
- to acknowledge the CTs' patients circuit within IPO-Porto;
- acquire the necessary knowledge to complete CRF's;
- contribute to the development of internal and/or external documents and understand its relevance in a clinical research centre;
- obtain an overview of the daily activities of GCP and Quality Management;
- understand the conduction and preparation of an audit;
- improve my communicational skills and practice medical writing skills.

1.3. STATE OF THE ART IN ONCOLOGY AND PHARMACEUTICAL R&D PROCESS IN EUROPE

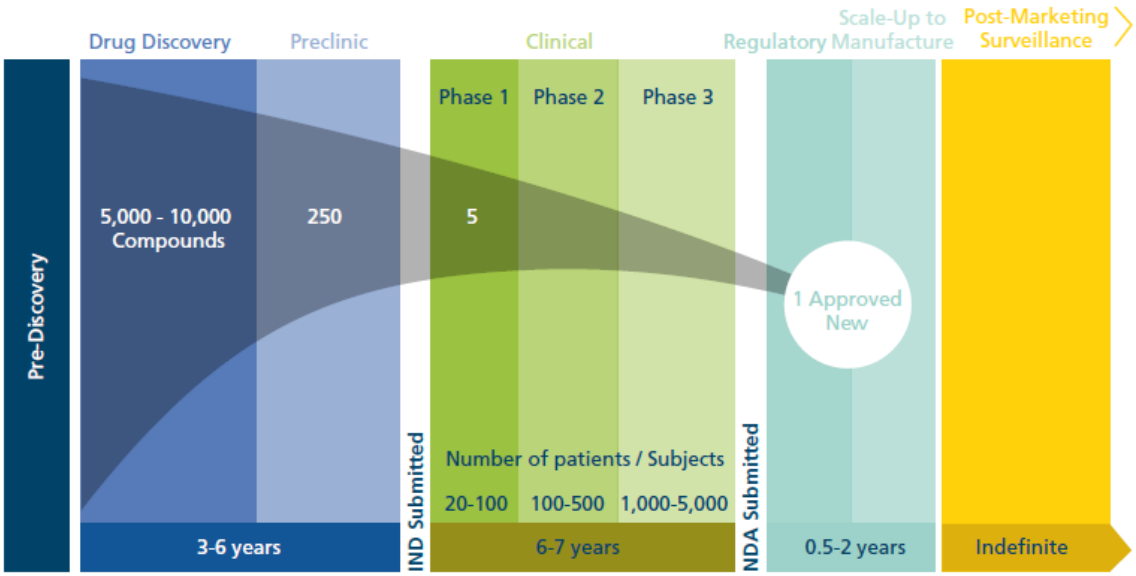
This section presents an overview of the current situation of the Pharmaceutical R&D and oncology research processes, and an overview of the CTs' Classification. Also, it briefly describes the state and particularities of the Oncology Clinical Research, referring considerations about special populations, that are a reality in the daily context of activities in Oncology Clinical Research.

1.3.1. Current concepts of the Pharmaceutical R&D Process

Biopharmaceutical research has provided new treatments, and potentiated by knowledge and technology, mortality has been reduced and the quality of life has been increased (16, 17). People now live longer and healthier, due to the wide availability and accessibility of treatments. However, there are pathologies that still entail great challenges to the R&D process, such as some type of cancers and orphan diseases (16, 17). In addition, the current process of Pharmaceutical R&D is considered unsustainable (18, 19), thus its paradigm is being changed, to continue delivering innovative medicines (18, 19).

R&D expenditure has increased, due to the high attrition rates, the cost of larger CTs, and the volume of resources required to get approval by regulatory authorities (16). Before a new chemical entity shows results proving failure, it usually reaches an advanced stage of research (16). Also, many medicinal products enter research, and few become a marketable product (Figure 3), increasing the attrition rates (17), due to the weak predictability of safety and efficacy (20). One of the reasons to the lack of efficacy in some therapeutic areas is the unpredictable results from animal models, i.e., non-correspondence between the effects obtained in animal models and those obtained in humans, leading to higher failure rates in Phase II and III trials (20). A huge investment is done, in order to develop one valid product. Besides, the R&D process is extremely slow (Figure 3): it is estimated that a product takes about 12 to 13 years to enter the market (17, 18).

Figure 3. Pharmaceutical R&D process timings and success estimates (18)



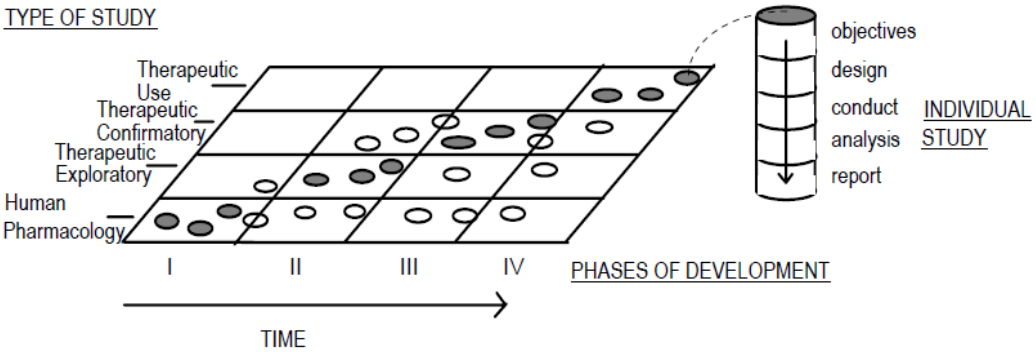
Before an IMP enters the clinical development phase, it is estimated that it passes the pre-discovery and discovery phases, when 5,000 to 10,000 compounds are screened. Most of those compounds are eliminated and about 250 are selected for the preclinical phase (non-clinical phase, conducted *in vivo*) (18). Up to this point, 3 to 6 years have passed. Of the preclinical tests, 5 IMPs are selected and submitted as an Investigational New Drug, entering phase I CTs (18). The CTs may take up to 6 to 7 years, until a New Drug Application is submitted. Only 1 IMP receives approval, and 9 to 13 years may have passed (18). Furthermore, general population may have access to the new drug only 0.5 to 2 years after its approval (18). The failures related to efficacy and safety issues redirect to the need of changing the R&D paradigm, through the development of more predictive models and proof of concept earlier in development, delivering innovation to unmet medical needs (21, 22).

The new R&D paradigm exposes the need for a dynamic new strategy. Its goal is to obtain profound knowledge of the pathophysiology of the condition in study. This brings more confidence in the mechanism of action and safety, thus allowing a quicker progression of the R&D process (23). The use of bioinformatics, better evaluation tools, and knowledge management, are crucial requirements to the success of this promising new approach (21, 22).

In this ambit, it is important to understand how clinical drug development has been divided until now. This division is conventional, and classifies CTs in four temporal phases

(Phase I-IV). The results from each phase have been used to determine the design of the next phase (24). However, with the evolution of CTs, that classification is no longer accurate, since the same type of CT may occur in different temporal phases of the clinical development, with the conduction of adaptive CTs. Thus, a classification system based in study objectives is more adequate. The relation between these two classification systems is represented in Figure 4, and shows the overlap of the study types and temporal phases (25).

Figure 4. Different development phases and types of clinical studies (25)



The CT phases, objective and related study population are described in Table 1, with the commonly associated temporal phase.

Table 1. CT Phases objectives [adapted from (24, 25)]

Phase	Objectives	Study population
Human Pharmacology Phase I	To evaluate tolerability, safety, define pharmacokinetics and pharmacodynamics; explore drug metabolism and drug interactions and; estimate activity (24, 25).	Limited number of healthy volunteers; Patients if there are toxicity limitations, such as in cancer diseases (24, 25).
Therapeutic Exploratory Phase II	Phase IIa: To assess pharmacodynamics, pharmacokinetics and; dose–response relationships (24). Phase IIb: To evaluate the dose–response relationship, increasing the understanding of efficacy, safety and tolerability of the IMP (24).	Small numbers of patients with the disease under study (24)
Therapeutic Confirmatory Phase III	To confirm efficacy, safety profile; explore the dose–response relationship, and adequate basis for assessing the benefit–risk relationship to support marketing authorisation (25); allow the completion of the official product information (25).	Hundreds or thousands of patients, usually an international programme (24)
Therapeutic Use Phase IV	To refine dosing recommendations; identify less common AEs; monitor safety aspects or compare the drug with other therapies already on the market (25); broaden experience in every-day clinical practice (24).	Patients, with wider selection criteria (24)

To achieve the reformulation of the biopharmaceutical sector, a common effort must be carried between industry and academy, on the pre-competitive research phase, concerning the globalization of knowledge, which will lead to innovative new therapies (19, 22).

1.3.2. Current European R&D Process

There is currently an European initiative coordinated by both pharmaceutical industry and regulators, aiming to modernize the current R&D paradigm: the Innovative Medicines Initiative (IMI), existing since 2008. The first IMI Scientific Research Agenda, published in 2008, had four research pillars: Safety; Efficacy; Knowledge Management; and Education and Training. As these pillars were broad, the revised IMI Scientific Research Agenda of 2011 replaced them with 7 focused Areas of Research Interest (19, 22):

1. The Patient in the Focus of Research: Development of drug research programmes focussed on the needs of the patients, with targeted outcome measures, and the participation of patient groups in consortia and development of partnerships (19, 22).

2. Diseases – Drug Efficacy: Development of new methods for evaluation and enhance of drug efficacy. Target the delivery of therapies, improvement of patient compliance, and generation of observational data earlier in drug development (19, 22).

3. Knowledge and Knowledge Management: Management of the knowledge generated globally, for ensuring the effective integration of data and maximisation of resources. Generation of knowledge, through the correlation of *in vivo*, *in vitro* and *in silico* research, while maintaining the sustainability of the databases (19, 22).

4. Strategies in R&D: Reduction of the attrition rate, through the modern 'omics'-focussed research combined with systems biology, leading to better understanding of the diseases aetiology (19, 22).

5. Drug Development and the Regulatory Framework: Development of evaluation and qualification tools and technologies for regulatory use. Addressing of challenges regarding chemical and formulation technology, in the context of regulatory aspects (19, 22).

6. Tools and Techniques: Identification, qualification and implementation of the tools and techniques developed for efficient R&D process (19, 22).

7. Education and Training: Science Communication: Spreading education and training, for reinforcing the position of the European scientific community in global R&D (19, 22).

In 2014, a Strategic Research Agenda for Innovative Medicines Initiative 2 (IMI2) has been published (18). The IMI2 agenda shapes the major challenges in the European healthcare system, pharmaceutical industry and the regulatory framework. In the IMI2 agenda, specific projects were not defined. Instead, strategies were identified and its adoption will lead to the creation of focussed and balanced projects (18).

The major goal of the IMI2 agenda is to deliver the background to start collaborative projects, allowing to approach and/or resolve bottlenecks on the delivery of effective and efficient healthcare to patients (18). The delivery of innovative solutions requires the union of know-how of academia, large and mid-size pharmaceutical and biotech companies, patient organizations, regulators, and health authorities and health technology agencies with the common goal of reforming and improving the current healthcare system (18).

The IMI2 defined 4 major axes of research, emphasising scientific challenges in which the collaboration of multidisciplinary stakeholders is crucial for success (18). The objectives/challenges of these 4 axes are described below.

Axis 1: Target validation and biomarker research (efficacy and safety)

To achieve better understanding of the pathophysiologic mechanisms, AEs, and the factors conditioning patients' individual responses to medicinal products. This will allow to obtain the knowledge and tools necessary to maximise the benefit of the treatment for the patient (18).

Axis 2: Adoption of innovative clinical trial paradigms

To sharpen up the concept of adaptive CT design, to minimise uncertainty in real world benefit/risk assessments of the new medicinal products, and to balance the need of data collection, regarding potential AEs (18). Also, to create more preventive approaches, and access of patients to medicinal products.

Axis 3: Innovative Medicines

To invest in strategies for early diagnosis and prevention, once there is an increasing incidence of chronic diseases and elderly population. There is now the goal of integrating therapies with prevention and healthy life style choices, and patients' education on health and their individual risk factors, to reduce the burden of diseases in society. Thus, there is

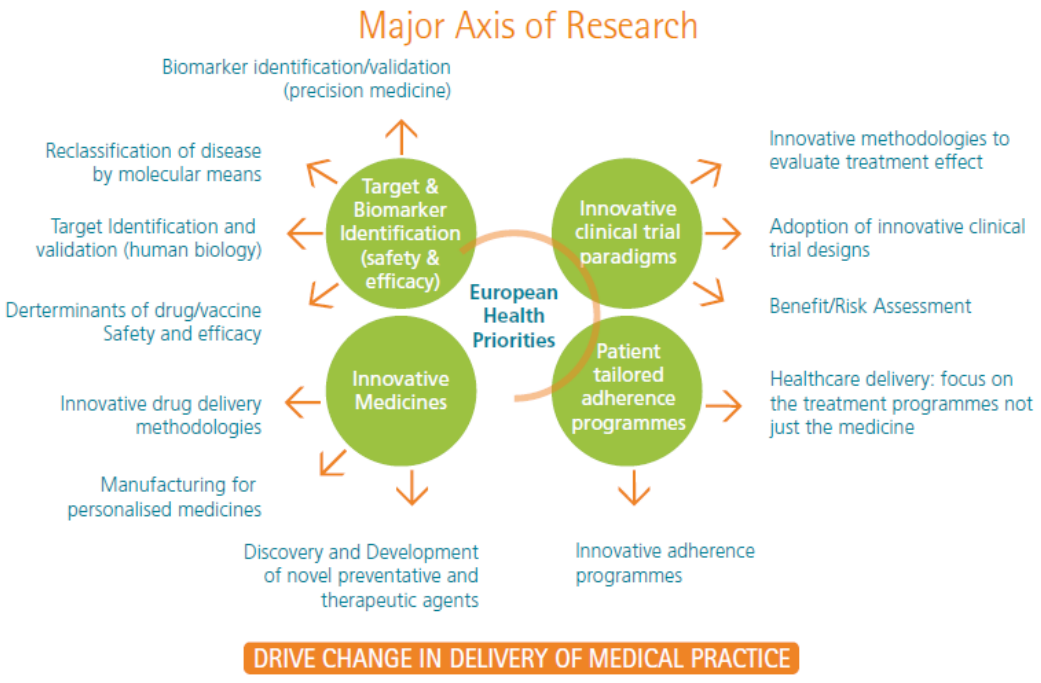
the need of the identification and each patient's risks and respective required intervention, minimising the occurrence of AEs (18).

Axis 4: Patient tailored adherence programmes

To study patients' life style, behavioural, societal and environmental factors, for the development of programmes, to maximise positive health outcomes and enhance drug adherence (18). This goal will take advantage of the new mobile technologies, customising intervention for individual patients (18).

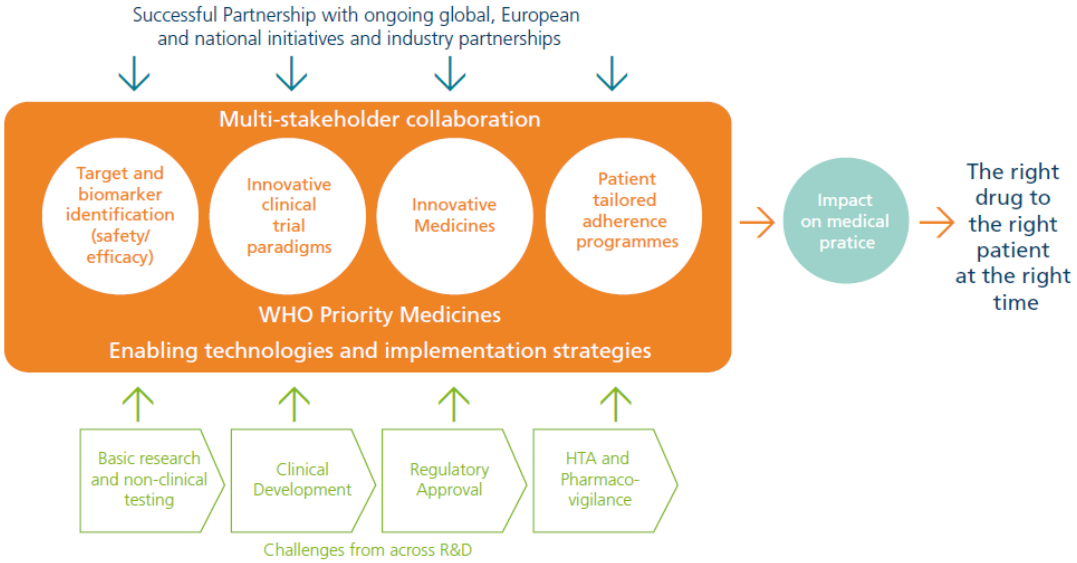
The 4 axes of IMI2 are summarised in Figure 5, presenting its action areas for the progress of R&D.

Figure 5. Integration of IMI2 Strategies in 4 Axes of research (18)



Each of these axes clearly identifies core objectives in the IMI2 Strategic Research Agenda to overcome challenges and achieve its goals. The aim and vision of IMI2 is "The right prevention and treatment for the right patient at the right time" (18) (Figure 6), as a continuation and progress of the IMI1. IMI2 pretends the delivery of effective and integrated healthcare solutions for priority medicines (18). For this matter, IMI2 will establish a partnership with ongoing initiatives, creating cross-disciplinary, international research (18).

Figure 6. IMI 2 summary: "The right drug to the right patient at the right time" (18)



1.3.3. Trends in Clinical Oncology Research

Regarding the anticancer drug development there is a high failure rate that needs to be addressed (26). It is estimated that about 95% of all IMPs tested in Phase I CTs fail to reach a marketing authorisation (26). Acting as predictors of success in CTs, new preclinical models can help reducing the attrition rate of new anticancer IMPs. Regarding the development phase, CTs should integrate predictive and pharmacodynamic biomarkers, driven by tumour biology. In the field of anticancer R&D, there is also the strong need of improving the collaboration between industry, academia and regulators, in order to meet the requirements of all stakeholders (26).

According to IMI2 Strategic Research Agenda (18), the prevalence of cancer diseases implies a considerable weight to the healthcare systems. Cancer patients need regular checkups and need to be medically followed for long-term conditions (18). The evolution of medical care, through diagnosis and treatment of cancer diseases, led to the increase of patients living with cancer. This, combined with the ageing of the population and risk factors such as exposure to tobacco smoke, lack of physical exercise and poor diet, triggers the increase of the incidence of cancer, which is expected to increase by 60 % over the next decade (18). European trends will be the aim of the following characterisation.

A recent article in the European Journal of Cancer (27), estimated, in Europe, in 2012, a value of 3.45 million new cases of cancer (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer (27). Female breast, colorectal, prostate and lung cancers are the most common in Europe, and represent half of the overall burden of cancer (27). Lung cancer is the cancer with highest mortality in men, while breast cancer is the cancer with highest mortality in women (27-29). However, it is estimated that this is changing for women: lung cancer may become the cancer with highest mortality for both genres, as lung cancer mortality is predicted to increase in women, while breast cancer mortality rate is predicted to decrease (28, 29).

As patients live now longer with cancer, the type of medicines needed has to equally evolve. There is now the need of assessing the benefit/risk relationship of the long term use of therapies (18). Also, there is the need for new biomarkers development for early diagnosis, and target therapies (18).

Oncology deals with many different cancers, which are genetically distinct. Each cancer responds to treatment combinations differently (30), and therapies for cancers diseases are complex, and often toxic (31). Cancers involve AEs caused by the disease and/or treatment, and frequently are associated with relevant co-morbidities (31).

Thus, oncology CTs may have innovative study designs, with exhaustive eligibility criteria, complex randomisation schemes and comprehensive treatment requirements, as well as AEs management specificities (31). The ideal investigational protocol in oncology should be flexible enough to adapt to patients' needs (31) (as sought by the personalised medicine area). These improvements in oncology R&D require the overcome of challenges regarding the regulatory approval of these therapies, as well as a thorough pharmacoeconomic assessment of these new technologies (18).

Furthermore, as reinforced in the IMI2, there is the need of constructing a platform that promotes and structures collaboration between all life sciences professionals and fronts, to achieve the common goal of finding "the right prevention and treatment for the right patient at the right time" (18, 32). This goal would benefit from the gathering of patients' tumour samples to characterise the molecular level of cancer diseases, allowing the improvement of diagnostic and statistical tests and the development of target agents for identifying molecular alterations (18). To overcome these challenges, a common effort has to be done between industry, hospitals, and academy, to maximise the use of the existing resources.

Regarding the contribution of CTs to the progress of oncology research, there is currently a consortium, the EurocanPlatform, aiming to use CTs and biorepositories data of patients, incorporating at the same time new imaging technologies for describing and characterising the tumours and treatment effects (18). Applying the IMI2 research axes to oncology, the following needs/objectives were specified, per applicable axis:

For Axis 1 - Target validation and biomarker research (efficacy and safety), the main aims are the: a) Reclassification of tumours on the molecular level; b) Identification of molecular targets in tumour formation; c) Integration of genetic analysis and tumour biology with bioinformatics and systems biology approaches to identify novel targets; d) Validated pharmacologically to accelerate drug development; e) High quality biomarker assays; f) Better understanding of histology-based and molecular-based tumour types and agree a standard of evidence to extend use of new medicines into other histology in patients with the same mutation (18).

For Axis 2 - Adoption of innovative clinical trial paradigms, the main aims are the: a) Validation of progression as a surrogate marker and analyse overall survival adjusting for unavoidable confounding factors; b) Agreeing on acceptable primary endpoint criteria for oncology CTs when overall survival is not a feasible endpoint; c) Development of markers of AEs with sufficient sensitivity and accuracy to support benefit/risk assessment; d) Better understanding of how the individual patient assesses the benefit/risk equation; e) Implementation of the new “Medicines Adaptive Pathways to Patients” initiative when applicable, to accelerate access to new treatments for unmet medical needs; f) Validated statistical methods for providing high quality results from post-marketing CT; g) Harmonization of trial procedures across Europe; h) Establish collaborative multicentre screening platforms, increasing efficiency of recruitment (18, 32).

For Axis 4 - Patient tailored adherence programmes, the main aims are the: a) Building of the outcomes of the “Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium” project to communicate the state of science and benefit/risk of new medicines to the patient in a common language; b) Development of approaches integrating prevention, early detection, susceptibility, and lifestyle changes; c) Establishment of continuous patient screening strategies combined with early CTs; d) Continue the early identification of relevant premalignant and malignant lesions, allowing chemoprevention (18).

Summarising, some of the current main challenges in oncology R&D are to obtain tools and competencies needed to support precision medicine approaches, pairing with

the required regulatory framework, an improved early detection and management of disease, and new therapeutic options personalised to tumour type, lifestyle and genetic susceptibility.

1.3.4. Special and vulnerable populations in CTs

"Some groups in the general population may require special contingencies because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of use of the dose or schedule of a drug compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion.", according to (25). Also, there is the need for specific ethical considerations related to the consent from vulnerable populations and the compliance with the specific procedures regarding vulnerable subjects (25). Several special populations can be identified: Pregnant women, nursing woman, children, geriatric patients, and patients from different ethnic groups (25).

Geriatric population frequently has associated comorbidities, and concomitant therapies increasing the risk of drug interactions (33). Therefore, it is crucial to have information about a medicinal product activity in the elderly (33).

Paediatric population require several considerations regarding CTs. Medicinal products developed for adults do not allow a correct inference of its activity in paediatric patients, even if its dose is adjusted. Thus, if a condition is anticipated to possibly occur in the paediatric population, a Paediatric Investigation Plan should be developed for that condition's treatment (34). Regarding CTs in children, special actions are taken, such as the minimisation of risk and distress (for example, reducing discomfort in invasive procedures through the use of local anaesthetics) (34). CTs in this population ensures that the patients have access to medicines appropriately formulated and evaluated for their use (34).

A type of patient considered to be vulnerable is a subject whose willingness to participate in a CT may be influenced by the expectation of benefits or a retaliatory response, from senior members of a hierarchy, depending on his/her answer (35). According to (35), an example may be a subject that is member of a group with a hierarchical structure, such as health students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and

prisoners. In addition, vulnerable patients may also be those with incurable diseases, in nursing homes, unemployed or impoverished persons, in emergency situations, belonging to ethnic minority groups, homeless, refugees, minors, and incapable of giving consent (35).

Special/vulnerable populations are a reality at IPO-Porto. These populations may also participate in a CT. An example is the paediatrics population (36), the geriatric, and vulnerable population.

2. Training activities

The traineeship at UIC can be divided into Generic Training and Specific Training. The generic training consisted in understanding aspects which are intrinsic and transversal to the study coordination daily routine and that are considered basic knowledge for performing study coordination in oncology. The specific training section describes the activities I performed as SC trainee at UIC, firstly without being associated to a specific clinic, and afterwards while being associate to the Pathology Clinics of Gynaecology, Lung, Paediatrics, Urology, and the Service of Intensive Care.

2.1. GENERIC TRAINING

As a SC trainee, I was already aware of the regulatory affairs regarding the Clinical Investigation applicable laws and regulations, and the submission process and approval of a CT. Activities conducted before the CT's approval will also be described in this section. Furthermore, I developed knowledge in specific classification systems, widely used on CTs performed at IPO-Porto. I also acquired skills and experience in web based Informatics Systems necessary to perform Electronic Data Capture and, Interactive Response Systems. This generic knowledge is described in the following sections.

2.1.1. Regulatory Affairs

The regulatory activities are not part of a SC's daily routine at UIC, as they are performed by the GCP and Quality Manager. However, in order to be able to properly perform the study coordination activities, I had to be aware of the applicable guidelines and regulations, and acquired training in GCP.

2.1.1.1. Legislation

The Clinical Investigation area is highly regulated. My traineeship did not involve acquiring knowledge of the applicable legislation. However, the regulatory affairs knowledge that is part of my academic background was remembered during the traineeship.

CTs on a medicinal product for Human use are currently regulated by the National Law "Lei n.º 46/2004, de 19 de agosto", based on Commission Directive 2001/20/EC, of April 4th and Commission Directive 2007/47/EC of 5 September 2007, the latest

concerning Medical Devices. The Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 establishes specific provisions regarding the conduct of CTs on human subjects involving medicinal products, relating to the implementation of GCP. This Directive does not apply to non-interventional trials.

During my traineeship, a new law in clinical investigation was published in Portugal—"Lei n.º 21/2014 de 16 de abril" (37)—and will be in force in June 2014. The new clinical investigation law will supersede the aforementioned "Lei n.º 46/2004, de 19 de agosto".

The main aspects changed in the new law are that it adds considerations about non-interventional CTs; creates the National Registry of CTs to facilitate submissions and make clinical investigation transparent; creates the National Network of Health Ethics Commissions to harmonise their evaluation; establishes competitive deadlines in the evaluation of CTs at the Comissão de Ética para a Investigação Clínica (National Ethics Committee for Clinical Research – CEIC)—30 days—and approval of CTs at Autoridade Nacional do Medicamento e Produtos de Saúde, I. P (National Competent Authority for Medicines and Health Products – INFARMED)—30 days; establishes a deadline for the Comissão Nacional de Protecção de Dados (National Commission of Data Protection – CNPD) approval—30 days; establishes deadlines for financial contract analysis at CTs sites—15 days.

The Commission Directive 2005/28/EC of 8 April 2005 lays down the principles and detailed guidelines for GCP as regards IMPs for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. This directive was transposed to the national decree-law "Decreto-Lei n.º 102/2007, de 2 de Abril".

In addition, "Portaria n.º 57/2005 de 20 de Janeiro" approves the functioning of CEIC, which ensures protection of participants' rights, safety and well-being during CTs. CEIC also does a previous evaluation and monitoring of all clinical trials on a medicinal product for Human use. CEIC assesses the relevance and design of the research protocol, the benefit-risk evaluation of the intervention, human resources and materials available in research centres, financial concerns, recruitment procedures, the procedure for obtaining informed consent, and the circuit and accessibility of the experimental drug.

CNDP is regulated the national law "Lei 67/98, de 26 de Outubro", and establishes guiding principles of the processing of personal data. CNPD deliberates data protection aspects of participants in CTs on its deliberation "Deliberação nº 333 / 2007". CNPD ensures the consent of the participants, as well as confidentiality concerns. The aforementioned laws are the essential for CTs conduction in Portugal.

2.1.1.2. Feasibility Questionnaires

The feasibility questionnaire is a document sent by the Sponsor to a specific e-mail for clinical studies (managed by UIC) (8). The questionnaire is answered by the appointed Medical Oncologist of the applicable Pathology Clinic. This document assesses the site's conditions to perform a CT. It asks about the site equipment (for example, refrigerator with adequate characteristics to keep biological samples), about the human resources availability, the recruitment potential, certification, and other issues that may apply. This document usually has up to a 5-day answering period, and a record of all feasibility questionnaires answered at IPO-Porto and respective answer date is kept by the UIC (8). An example of a feasibility questionnaire can be found at (38). If required by the Sponsor, a pre-trial qualification visit can be performed at IPO-Porto, to assess the conditions.

I received an informal lecture about this subject, performed by Joana Maia, PharmD, GCP and Quality Manager of UIC. During this lecture, I understood the UIC's intervention in feasibility questionnaires forwarding, and the importance of a timely answer and the characteristics a centre should have for its selection.

2.1.1.3. Clinical Trial Approval

First of all, the Sponsor confirms that IPO-Porto will participate in the CT, and sends a summary of the CT to the UIC. The summary is forwarded to the Medical Oncology Coordinator of the Pathology Clinic and to the Director of Service, to the Pharmaceutical Services, Day Care Hospital, and other applicable Services (such as Cardiology for ECGs or Nuclear Medicine for Bone scans). If the Medical Oncology Coordinator of the Pathology Clinic and the Director of Service have a favourable opinion on the proposed CT, a PI for the CT is suggested to the UIC. The UIC Responsible also emits an opinion and, if favourable, the PI is contacted to be informed about the summary of the CT and to decide about his/her participation. This has to be done in 5 working days (8). The Director of Service, the Pharmaceutical Services, the Day Care Hospital, and other applicable Services also emit an opinion and, if favourable, propose the elements that will be part of the CT team and inform the UIC. The PI proposes the CT team elements of his/her Pathology Clinic. The CT team is defined, and approved by the PI and the Responsible of UIC. This has to be done in 5 working days and the CT team is sent to the Sponsor (8).

After that, the PI fills the CT Submission Form, which is an internal document of IPO-Porto, containing the CT team, estimated costs and the aforementioned intervenients' opinion. This document is part of the submission dossier.

The GCP and Quality Manager verifies if the submission process contains all the mandatory documents required by IPO-Porto Administration Board and listed in (8), as well as study documents stated in the Sponsor's list of sent documents. It is also important to do quality control in this process. The GCP and Quality Manager also verifies if all the documents' versions are correct, as well as other regulatory data. The GCP and Quality Manager obtains a financial opinion from the Financial Assessor of CI-IPOP and approval from the AB. At IPO-Porto, the AB receives and verifies the submission process as soon as possible. This means that a CT may be ready for final approval at IPO-Porto even before it was approved by INFARMED and CNPD, or evaluated by CEIC, increasing IPO-Porto competitiveness as a clinical research centre. Instead of the final approval/evaluation documents, the Administration Board evaluates the submission dossier with a document confirming the CT submission to authorities. In this particular situation, when a CT is approved by the national authorities, the final documents are added to the submission process, and the CT becomes officially approved at IPO-Porto. The essential documents for conducting a CT are listed in (35).

Concerning other documents, the CT Contract is approved by the Administration Board after evaluation of the Responsible of UIC and the PI. The Financial Contract is evaluated by the Financial Assessor of CI-IPOP and the Responsible of UIC.

I received an informal lecture about the Submission Process, performed by Joana Maia, PharmD, GCP and Quality Manager of UIC. During this lecture, I understood the UIC's intervention in submission processes, and the role of the Administration Board in its approval.

2.1.1.4. Guidelines

The Declaration of Helsinki is a very important document, and states the core of CTs: The patient should never be harmed in any way in favour of public health or society (39). During the traineeship, a new version of the Helsinki Declaration was published, with a new organisation of its structure (39). Being a world reference, the 2013 Declaration of Helsinki replaces the previous versions of the declaration, having clarified the patients' protection in the conduct of CTs (39). The main changes of the 2013 declaration are that:

- there should be a risk minimisation and continued monitoring and assessment while the study in ongoing (39);
- subjects should be compensated appropriately of harm caused by the participation in a CT (39);

- the patients should always receive the best available intervention when not in the IMP study arm (39);
- the placebo use should be well justified, and only if there is the need to determine the safety or efficacy of an intervention, there is no active treatment available, or if it is proven that the subjects will not be harmed in any way by not receiving the treatment (39);
- the patients that benefit from the CT intervention and still need it after the trial, should have access to it, and this information should be disclosed in the Informed Consent Form (ICF) (39).

The "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) makes recommendations towards harmonising the interpretation and application of technical guidelines and requirements for pharmaceutical product registration (40). This harmonisation is achieved through the development of ICH Guidelines (40).

One of the most important guidelines when conducting a CT—the ICH E8 Guideline—addresses General Considerations for CTs. Additionally, a crucial document is the ICH E6 Guideline on GCP, which establishes principles to be followed in the conduct of CTs, improving Clinical Research.

Other important guidelines to be aware of, in oncology CTs, are those with considerations based on agreed ethical and scientific principles, for clinical testing programs conducted in special populations, such as ICH E7 for geriatric populations (33), and E11 for children (34).

During my training in study coordination, I remembered the concepts and specifications of these guidelines that I already had present from my academic background.

2.1.2. Good Clinical Practice

The GCP training is an essential requirement to perform Study Coordination activities. Thus, as a SC trainee, I did an online training in GCP, where I reviewed the knowledge acquired in the MSc course, and acquired a certificate in ICH-GCP (E6 Guideline). The GCP guideline is a standard for the design, conduct, performance, monitoring, audit,

record, analysis, and report of CTs. There are 13 GCP principles presented in the ICH-GCP Guideline (35), which should never be forgotten while conducting a CT.

2.1.3. Classification Systems

The knowledge I acquired in classification systems concerns specific tools used in oncology CTs: Cancer Staging; Performance Status scales; the "Common Terminology Criteria for Adverse Events" code and; Tumour Response Evaluation criteria.

Although these classification systems are applied by the Investigator, understanding the applicable classification systems was very useful to me, when collecting the patient's data.

2.1.3.1. Cancer Staging

Understanding cancer staging is important, since this knowledge patient's may estimate a patient's prognosis and help planning his/her treatment (41). Staging systems are still evolving and are particular for some pathologies (41).

As described by the "National Cancer Institute", the TNM staging system reflects the site of the primary Tumour (T) and its size and/or extent, the spread or not to nearby lymph Nodes (N), and the number of tumours and Metastasis (M) (41). The TNM designation is applicable to most types of cancer. However, for example, breast and prostate cancers have their own grading systems (42).

In the context of the Pathology Clinics where I developed my traineeship, I also acknowledged other classification systems:

- The "International Federation of Gynaecology and Obstetrics" staging, also based on the TNM system, regards cancers of the cervix, uterus, ovary, vagina, and vulva (41). This system is applied on the Pathology Clinic of Gynaecology.
- The Gleason score, used to grade prostate cancer in the Pathology Clinic of Urology, based on biopsy samples taken from the prostate gland (42).
- The Children's Oncology Group staging (41), used in the Pathology Clinic of Paediatrics.

The cancer stage is an important eligibility criterion when screening a patient for a CT.

2.1.3.2. Performance Status

The most used scale for assessing a performance status is the Eastern Cooperative Oncology Group (ECOG) performance status. This performance status assessment consists of how a disease is progressing, and how the disease affects the patient's daily life activities (43). A lower score reflects the greater ability of the patient to perform daily life activities. Another scale is also used in some CTs: the Karnofsky Performance Status. A higher score mirrors the patient's ability to carry out daily life activities (44). The Lansky Scale is the Karnofsky scale applied to people under 16 years old (45). Figure 7 presents a table with the equivalence between the aforementioned scales.

The performance status evaluates the patient's wellbeing, which is an important data to be collected, and may also be an eligibility criterion for entering a CT. I acknowledged these scales in my daily routine activities.

Figure 7. Conversion Table from ECOG to Karnofsky/Lansky Scales (45)

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

2.1.3.3. Common Terminology Criteria for Adverse Events v 4.0

The National Cancer Institute "Common Terminology Criteria for Adverse Events" (46) is a useful tool widely used in Oncology CTs to report AEs. It consists of a descriptive terminology organised by System Organ Class, and associated to grading scale on severity for each AE term (46). Each term represents a specific event, used for reporting. The last available version, and most used, is v4.0, which grading is represented in Table 2 (46). However, there are some CTs still using the version 3.0. In those CTs I had to consult the v3.0 in order to perform data entry activities accordingly.

Table 2. General guideline for AE severity grade [adapted from (46)]

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.

This was a very important tool to acknowledge, since a SC has to report AEs to the Sponsor. This data has to be recorded in the patient's PHR, in order to be reported in the CRFs. Nevertheless, understanding this classification system is very useful when reporting an AE. Also, a SC may help the Investigator to comprehend this system, as it is not mandatory in the normal clinical practice.

2.1.3.4. Tumour Response Evaluation

The "Response Evaluation Criteria In Solid Tumours" v1.1 (47) is a set of published rules, by an international collaboration, that define the response of cancer patients to treatments, through image assessments. These criteria are widely used both in adult and paediatric CTs (48). They objectively assess the response of measurable lesions, non-measurable lesions, target lesions, and non-target lesions (47). Other criteria for

evaluating tumour response are those published by the World Health Organisation, by evaluation of change from baseline while on treatment. However, these criteria have been modified over the time and are often considered confusing (48). While reporting data to the Sponsor, it is important to understand these response evaluations, to ensure that the reported data is accurate and correct.

The Prostate Cancer Clinical Trials Working Group 2 has recommendations, for the evaluation of bone scans, widely used in Prostate CTs. According to this group, if the bone scan indicates progression, and there are not any other exams supporting progression, it should be considered progression when at least two or more new lesions are observed on bone scan, compared with the baseline scan (49).

2.1.4. Case Report Forms

To record the CT's data in the Sponsor's database, it is required training and skills in "Electronic Data Capture" systems, called "Electronic Case Report Forms" (e-CRF). Thus, as SC trainee, I performed trainings, to be skilled in systems such as: Medidata Rave® (50); Inform™ (51); Oracle® (52) and; Datatrack™ (53). The training I received was either in online training systems or orally, and lectured by my supervisor. These systems enable the record of information on the patient to the Sponsor, according to each investigation protocol (54). Thus, these systems are adapted to each CT, and its use ends up being intuitive. The e-CRF completion allows the capture, review, management, storage, analysis, and report of data, in a systematic basis (54).

In CTs performed years ago, this data recording systems were not electronic, they consisted of proper paper forms provided by the Sponsor. I had the opportunity of consulting one of those CRFs. The e-CRFs facilitated the archive and transport of data, since these data capture systems can be very extensive and the online systems save a huge amount of paper and time.

Understanding the aforementioned systems is very important, to report the patient's data with accuracy. The activities concerning data reporting will be detailed in sections 2.2.1.7 and 2.2.1.8.

2.1.5. Interactive Response Technology

Interactive Response Technology provides automated confirmation of assignments, both to the centre, in order to proceed with the assignments; and to the Sponsor, functioning as a regular reporting of CT activities progress (55).

This technology can be an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). These systems are used by the SC to screen the patient (after that, the patient can start the screening procedures); randomise the patient (assignment to the study treatment arm); assignment of study visit, to dispense the study medication; and to discontinue the patient's treatment. Screening failures are also registered in the IVRS/IWRS system. Furthermore, these systems are used to manage kit supply, acknowledge study drug receipt, and register an unscheduled visit.

IVRS consists of an automated phone call, by steps, and provides automated confirmation of assignments via fax. IWRS consists of an intuitive online system, and provides the confirmations via e-mail or in the online system itself (55). The IWRS allows users to observe the study progress, which is an advantage comparing to the IVRS (55).

I had the opportunity to acknowledge different IVRS/IWRS technologies, such as ClinPhone, ICOPhone, Almac, Bracket, IRT. Understanding this technology is important to perform these tasks efficiently. I observed these systems being used several times during my traineeship, and they are very intuitive.

2.1.6. Standard Operating Procedures

In the final stage of the traineeship, I was enrolled in the activity of writing four Standard Operating Procedures: Pre-screening; Screening; Randomisation/Treatment Initiation; and Study Termination. This activity included the development of flowcharts describing these procedures.

The general objective of the procedures was to harmonize the activities performed in each stage of the CT. The procedures define responsibilities and a list of the steps of the activities that are assigned to the team member, at IPO-Porto and according to GCP. The procedures apply to the elements of the CT team that participate in each stage, primarily to the Investigators and SC. The documents have been submitted and revision (and subsequent approval) is pending.

2.2. SPECIFIC TRAINING

The study coordination activities developed at UIC will be presented by chronological order in which they were performed. This order reflects a growing degree of specificity, and responsibility of the tasks within UIC. Every activity I performed was supervised, and corrected or improved when needed. At first, I started assisting the Pathology Clinics of Digestive and Lung. After that, I started assisting the clinics of Lung, Gynaecology, Urology and Paediatrics.

2.2.1. Initial Training Activities

At the beginning of my traineeship, I did mainly organisational activities, which allowed me to understand the role, importance and the articulation of each document at UIC, and where I could find them. I understood that, when conducting a CT, "what is not written, did not happen". Thus, it is crucial to keep records and maintain them up-to-date.

After these activities, I accumulated other tasks, related with the files aforementioned in the dossiers' description, such as processing the patients' expenses, preparation of study visits, and schedule of exams and visits. I then started participating in other type of activities, such as data reporting, assistance to monitoring visits and site initiation visits. These activities are transversal to all CTs.

2.2.1.1. Dossiers

The dossiers that are part of a SC daily routine and with which I worked were:

- **The Investigator's Site File**

This dossier is provided by the Sponsor and contains all the information on a CT, namely the Investigation Protocol and further amendments (when applicable), the Investigator's Brochure, ICFs (updated and obsolete versions), Laboratory Manual, CRF Completion Guidelines, Delegation Logs, Curricula of the CT staff, Training certificates, correspondence, and all information that may apply.

I archived documents in the File, in the proper section. Also, I identified if there was any section with missing information and documents, so that they could be requested and properly archived to complete the dossier. This activity allowed me to understand what type of documentation a SC has to gather after a CT's approval and the timelines for those activities. This also helped me to understand the importance of updating the

documents, such as new versions of the Protocol or of the ICF. For example, when there is a new ICF, it has to be archived in the Investigator's Site File, and a copy of the obsolete versions must remain there, properly identified with the word "obsolete", so that the old versions are not used. Regarding this particular case, every superseded document has to be replaced in other dossiers, such as the workbook, so that no old versions are used.

- **The Workbook**

This dossier consists in a compilation of the everyday material of a CT (in blank), being used for the patients' visits. It may be provided by some Sponsors, or may be organised from scratch by the SC. Although not mandatory, this dossier is very helpful and practical when scheduling and preparing the patients' visits. The type of materials found in a workbook are usually: ICFs, Eligibility Criteria worksheets, Screening and Randomisation worksheets (if required), Prescription sheets (IPO document), Exams requisitions (usually provided by the Sponsor), IP administration worksheets (for intravenous administration) or the medication diary (for oral medication), AE diaries (if applicable), and any other document that may apply to a given CT and that is mandatory to be filled in the patients' visits. These materials should always be updated if there is any further version or amendment of the same.

I completed workbooks, starting with the organisation of the study materials of two CTs from the Digestive Clinic. As these CTs had several study materials, I added an index to each workbook, to facilitate its navigation. This activity allowed me to familiarise with the type of study documents that are part of the routine of patients' visits and to understand the SC's role in ensuring that every necessary material is available for completion during the patients' visits.

- **The Patient's File**

This dossier may be provided by the Sponsor in some CTs. However, UIC has its own organisation, regarding this dossier. This dossier contains the patient's data, regarding his/her participation in the CT. The following data can be found in this dossier: ICF (original, if not required to be archived in the ISF by the Sponsor), Screening and randomisation confirmations, exams' requisitions and respective confirmations, copy of IMP prescriptions and confirmation of medication dispensing (when applicable), local laboratory analysis reports, clinical diary (recorded by the investigator in each study visit) and follow-ups, End of Treatment confirmation, SAE reports if applicable, other information specific of each CT such as questionnaires and medication or AE diaries.

Besides organising this dossier for new patients, I also archived data on existing dossiers and identified the need for updating data or ask for validation (investigator's signature). This activity allowed me to understand the main data to gather and keep up to date concerning the patient's participation in the CT, as well as the data that should be available for the monitoring visits and CRF completion.

- **The Patient's Personal Health Record**

The PHR gathers the patient's data at IPO-Porto since his/her registration at the institution (excluding data that is electronic). When in a CT, the patient's PHR is identified as belonging to UIC. This means that when not in use in other departments of IPO-Porto, the PHR should be archived in UIC's facilities. Also, a label is added to the PHR, so that other departments easily acknowledge that the patient is participating in a CT. the following data concerning the CT is present in the PHR: ICF (copy), record sheets from UIC, prescription sheets, IMP administration worksheets or other nursing records, dipstick analysis report, Imaging reports (such as Computed Tomography or Bone scan), and central laboratory analysis reports.

This is the file that serves as contact between UIC and the Pathology Clinics, or the Day Care Hospital and central of analyses, and that circulates within IPO-Porto facilities. My role was archiving and verifying the data. I realised the importance of the filling of those materials and the SC's role in ensuring that every necessary material is complete and accurate.

2.2.1.2. Processing the patients' expenses

Complying with the legislation, the patients participating in a CT have the right to be reimbursed for his/her participation in the CT, in regard of the expenses of the patient's traveling for the study visits and meals (or eventually AE management medication). For this matter, UIC has a form where the expenses are described, for further verification by the financial assistant and analysis by the Sponsor, whom reimburses the patient.

The patient delivers his/her expenses to the investigator, who forwards it to UIC. As a SC trainee, I received the patients' expenses and matched the date of the receipts with the study visits the patient performed, detailing this data in the form. This procedure justifies the patient's expenses, ensuring they are related with the CT. If there are any receipts that do not match any study visit in any way, those receipts are forwarded to the patient. After completing the form I anonymised the receipts related with study visits, and forwarded them, with a copy and the form verified and signed by the SC, to the financial

assistant. This is an important procedure, since data that could identify the patient cannot be sent to the Sponsor.

2.2.1.3. Preparation of study visits

The PHR is the contact point between UIC and other departments. When a patient has a scheduled study visit, the SC prepares the patient's PHR with the data that needs to be collected by the Investigator and nurses. My role was to compile all the documents that needed to be filled on that given visit according to the protocol, which are present in the workbook (these forms are aforementioned in section 2.2.1.1, regarding the workbook). Thus, I gathered the blank forms of that given CT and filled the patient's number and other applicable data (for example: name, date of birth, number of visit, date). I also composed a UIC's record sheet, listing the procedures that needed to be performed on that visit per protocol, and what should be scheduled for the following visit.

2.2.1.4. Agenda of UIC

For UIC's internal organisation of activities, a calendar is made every month, recording the patients' visits. Each coordinator records the activities referring to the respective Pathology Clinics. The calendar is also sent to the Study Nurse responsible for taking patients' biological samples, detailing the patient's study visit number. I had the opportunity to complete the calendar, recording the activities of the Pathology Clinics of Digestive and Lung, in given months. This improved my organisational skills and made me realise the workload of a SC and some of the aspects that are part of a SC's daily routine.

Another agenda that is kept is the monitoring visits schedule. This is important for the management of UIC's facilities, since it has to be ensured that the offices are ready for the monitoring visits, with the necessary materials available for the visit. The SC schedules the visits and the operational assistant prepares the monitoring offices.

2.2.1.5. Schedule of patient's exams

Regarding the schedule of patient's exams, it is very important to comply with the protocol requirements, so that there are no protocol deviations. Also, the cooperation of the laboratories is crucial, ensuring the results are available on time. Regarding the study visits scheduling, some of the Pathology Clinics implemented a system of reserving a number of vacancies specific for CTs. This ensures compliance with protocol. As a SC trainee, I scheduled imaging exams. For that, I sent the exam requisition signed by the Investigator to the imaging laboratory, by fax. Then, I received the confirmation with the

scheduled event, complying with the time window I requested. If needed, I would telephone the contact person in the laboratory to schedule the exam. Then, I would contact the patient and let him/her know the date of the exam.

While performing the activities mentioned in the last sections, it is essential to have attention to detail, so that no mistakes are done. I understood the functioning and organisation of UIC, and what is needed to perform a SC's tasks rigorously and on time, always complying with the protocol and GCP.

2.2.1.6. Training challenge

With the evolution of UIC, the scheduling and archiving tasks were assigned to the CTA. However, these are very important tasks to be familiarised with, since they show the organisation and functioning of UIC.

During my traineeship, two CTAs joined the UIC's team. I had the opportunity to accompany one of them for a brief period of time, helping her to familiarise with UIC's procedures. This was a challenging opportunity that tested my knowledge and communication skills, since I had to convey the learning I had received until then.

2.2.1.7. Completion of e-CRFs and queries resolution

E-CRF completion activities allow the Sponsor to access the patients' data, regarding the CT. The data usually reported in the e-CRF concerns medical history, demographics, diagnosis, study medication dispensing, date of study visit, laboratory results, imaging results, AEs, concomitant medication, questionnaires and other data that may apply.

Data is available in the PHR and should by reported within the timelines defined in the protocol (usually within 5 days after the study visit). Before entering the data in the e-CRF, I verified if it was complete, so that amendments could be done if necessary. Understanding the classification systems mentioned in the generic training section was very useful when filling e-CRFs. I had the opportunity of performing data entry and query resolution in e-CRFs of the Pathology Clinics of Digestive, Lung, Gynaecology, Paediatrics and Urology. E-CRF completion ends up being an intuitive task.

After data entry, queries may be generated (automatically, or by CRA, Data Manager or Medical Manager). Usually, queries have a response period of 5 working days. If they are automatically generated, they should be addressed immediately. It is important to answer in time, in order to clarify any doubts regarding the data.

Regarding the e-CRF completion activities, I also had the opportunity to prepare an interim analysis and database lock. The preparation of interim analysis and database locks imply that all the subjects' data is recorded in the e-CRF, and all queries are answered, according to the established timelines.

The e-CRF activities allowed me to test my time management skills and aptitude of complying with deadlines. The activities I performed were supervised.

2.2.1.8. Serious Adverse Events Reporting

SAE reporting was another important activity regarding the data to be reported. A SAE must be immediately reported to the Sponsor (35), and as defined by the protocol timelines: usually 24 to 48h after its acknowledgement. This procedure may require a form filled by the Investigator, reporting the SAE, and sent to the Sponsor, or may be reported by the SC in the e-CRF. If the SAE is reported in a paper form, queries may be received and answered afterwards by the same system (usually fax). I have reported SAEs in e-CRFs, and answered to queries related to them. This activity was supervised, and done in the Pathology Clinics of Lung and Paediatrics.

2.2.1.9. Site Initiation Visits

I had the opportunity to participate in 8 Site Initiation Visits, so that I would have an overview of different phases and Pathology Clinics of CTs conducted in IPO-Porto. These data are resumed in Table 3.

Table 3. Participation in Site Initiation Visits, per Pathology Clinic and type of study [adapted from (56)]

Pathology Clinics	Number of Initiation Visits	Type of study
Breast	1	Phase II
Digestive	2	Phase II; Medical Device
Intensive Care Service	1	Phase III
Lung	2	Phase II/III; Phase III
Onco-Haematology	1	Phase III
Soft Tissue and Skin	1	Phase I

These visits are usually specific for the Investigators and SC, study nurses, and pharmacists. The CRA conducts the initiation visits, for each team, on the scheduled dates. The following aspects are presented in site initiation visits for Investigators: a) Study objectives; b) Endpoints; c) Eligibility Criteria; d) Study Design and plan; e) Screening procedures; f) Randomisation procedures; g) Study procedures; h) Safety activities; i) End of Treatment; j) Follow-up activities and End of Study; k) Study withdrawal; l) AEs and SAEs Management and report; m) Investigator Responsibilities.

At the end of the presentation, the investigators clarified their doubts, and signed the delegation log. Then, the CRA provided the study materials to the SC: Patients' Files with ICFs, patient cards, AE diaries and record worksheets. Furthermore, documents were organised and archived in the Investigator's Site File. Additionally, the SC's usernames and passwords for the IVRS/IWRS and e-CRF were provided.

The CRA also schedules a meeting for the study nurses, regarding CT procedures, such as sample collection and IMP administration procedures, as well as issues related with the record of data. I participated in one study nurse initiation visit. This visit was focussed in the IMP administration and samples' collection and processing. Also, the material for that purpose was installed, and the central laboratory kits, manuals and shipping materials were provided.

During my traineeship, the chief-Nurse of Day Care Hospital, where the intravenous IMP is administrated, identified the need to implement a checklist for these visits. This checklist would be delivered to the CRA, before the initiation visit, as a suggestion of issues to focus in the visit at the Day Care Hospital. Thus, the CRA could be well prepared for the needs of the Day Care Hospital, and could know in advance the number of nurses present, the schedule for the visit, as well as the place where it is conducted (these aspects are standard for all visits). The issues that should be addressed are:

- Study design;
- Eligibility criteria;
- Administration procedures (IMP and/or other medicines);
- AEs related to the IMP that are predicted to occur, and its management (prophylaxis and treatment);
- Hypersensitivity/allergic reactions that may occur and its treatment;
- Record sheets ;
- Written information regarding the CT.

This checklist will be sent to the CRAs, whenever a new CT initiates at IPO-Porto, to improve its efficiency. Another initiation visit is conducted in the Pharmaceutical Services, regarding the preparation of medication and supplies, as well as specific documentation. These presentations serve as training, and the CT team has to be properly trained before starting the CT activities.

2.2.2. Pathology Clinics Specialisation

As my traineeship evolved, I got enrolled to the study coordination activities of the Intensive Care Service and the Pathology Clinics of Lung, Gynaecology, Urology, and Paediatrics. The CTs in which I participate were all sponsored by the industry, and all Prospective, Multi-Centric and Multi-National (except MuTAR, which is National). In this context, I briefly describe the CTs in which I was involved, in the Pathology Clinic of Urology (Table 4), in the Pathology Clinic of Lung (Table 5), and in the Pathology Clinics of Gynaecology, Paediatrics, and the Intensive Care Service (Table 6).

Table 4. Urology Clinical Trials [adapted from (56, 57)]

CT Acronym (EudraCT Number)	**Purpose**	**Study Design**
C21004 (2010-018661-35)	To compare Orteronel plus Prednisone vs Placebo plus Prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer	Randomised, Double-Blind
C21005 (2010-018662-23)	To Compare Orteronel plus Prednisone vs Placebo plus Prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or following Docetaxel-based therapy	Randomised, Double-Blind
FIRSTANA (2010-022064-12)	To compare two doses of Cabazitaxel in combination with Prednisone vs Docetaxel in combination with Prednisone, in patients with metastatic castration-resistant prostate cancer not pre-treated with chemotherapy	Randomised, Open-Label
LATITUDE (2012-002940-26)	To compare Abiraterone Acetate plus low-dose Prednisone plus Androgen Deprivation Therapy (ADT) vs ADT alone in subjects with high-risk metastatic prostate cancer not pre-treated with hormonotherapy	Randomised, Double-Blind
METEOR (2013-001010-14)	To compare Cabozantinib vs Everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Randomised, Open-Label

Regarding the CTs conducted in the Pathology Clinic of Urology (Table 4), most of them were for prostate cancer. Only one was for renal carcinoma, which was a novelty, since there were not any CTs for the kidney at IPO-Porto. Regarding the CTs C21004 and C21005, I only had the opportunity to participate in a small number of activities, since the patients' visits were not very regular. Regarding FIRSTANA, I participated in many tasks, although the number of patients included in the CT was bigger for patients in follow-up. I participated in several monitoring visits and had the opportunity to prepare the e-CRF for an interim analysis. LATITUDE was the CT of this clinic in which I performed more variety of activities, and contributed the most. METEOR started during my traineeship. Thus, I had the opportunity to accompany the initiation of a CT in this clinic.

Table 5. Lung Clinical Trials [adapted from (56, 57)]

CT Acronym (EudraCT Number)	**Purpose**	**Study Design**
1200.55 (2009-017661-34)	To assess afatinib in 1st line or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer harbouring EGFR mutation(s)	Open-Label
Ideate (2009-017396-19)	To compare the efficacy of Ipilimumab plus to Paclitaxel and Carboplatin vs Placebo plus Paclitaxel and Carboplatin in subjects with stage IV/recurrent non-small cell lung cancer	Randomised, Double-Blind
LUX-Lung 8 (2011-002380-24)	To compare afatinib vs Erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy	Randomised, Open-Label
MK-3475-010 (2012-004391-19)	To compare two doses of MK-3475 (SCH900475) vs Docetaxel in previously treated subjects with non-small cell lung cancer	Randomised, Open-Label
MuTAR (2010-022509-17)	To assess Erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor.	Open-label

Concerning the Pathology Clinic of the Lung (Table 5), I accompanied CTs that were in its last phase within the study coordination context (LUX-Lung 8), CTs that were active when I started the traineeship (Ideate and MuTAR), and new CTs, that I accompanied since the site initiation visit (1200.55 and MK-3475-010). The new CTs and Ideate were the CTs in which I most contributed.

Regarding the Pathology Clinic of Gynaecology (Table 6), I verified that the staff was familiarised with the procedures. This aspect mirrors the CTs situation: the CTs are conducted at IPO-Porto since years ago, and the treatment period is long.

Table 6. Other Pathology Clinical Trials [adapted from (56, 57)]

CT Acronym (EudraCT Number)	**Purpose**	**Study Design**
Gynaecology		
ROSiA (2010-019525-34)	To assess the addition of Bevacizumab to Carboplatin and Paclitaxel as front-line treatment of epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma	Open-Label
TRINOVA-1 (2010-019821-32)	To compare Paclitaxel plus AMG 386 vs Paclitaxel plus Placebo in women with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers	Randomised, Double-Blind
Intensive Care Service		
INHALE 2 (2008-000906-35)	To evaluate the safety and efficacy of BAY 41-6551 as adjunctive therapy in intubated and mechanically-ventilated patients with gram-negative pneumonia	Randomised, Double-Blind
Paediatrics		
MK-0517-029 (2012-002340-24)	To evaluate the pharmacokinetics/pharmacodynamics, safety, and tolerability of Fosaprepitant in pediatric patients for the prevention of chemotherapy-induced nausea and vomiting (CINV) associated with emetogenic chemotherapy	Randomised, Partially-Blinded
Unspecified		
MK-0517-031 (2012-001718-41)	To examine the efficacy and safety of intravenous Fosaprepitant Dimeglumine for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy	Randomised, Double-Blind

Regarding the Pathology Clinic of Paediatrics (Table 6), I verified that the Investigational Team was still getting used to CTs, and is still evolving. The same was verified in the Intensive Care Service (Table 6). These clinic and service have a few specificities related to the patient populations that will be further discussed in this report. For this reason, the Investigational Teams also needed more support.

In addition to the activities I already had performed in these clinics, I started participating in monitoring visits and assisting to patients' clinic visits when possible. I also had the opportunity of sending biological samples for the patient's screening. These activities allowed me to understand the patient's circuit within IPO-Porto, and some of the oncology specificities.

During my traineeship, I did many tasks, whenever they would surface (as previously mentioned). For this reason, those activities were not developed according to a normal CTs' conduction order, but according to the situation when they would be needed. Figure 8 presents a flowchart describing the order of the CTs' tasks conduction in each patient visit at IPO-Porto, if we would consider a single CT from its initiation at the site until its termination, from the SC's perspective. The activities I performed in each CT are described in Table 7.

Figure 8. Study Coordination activities sequence per stage of CT

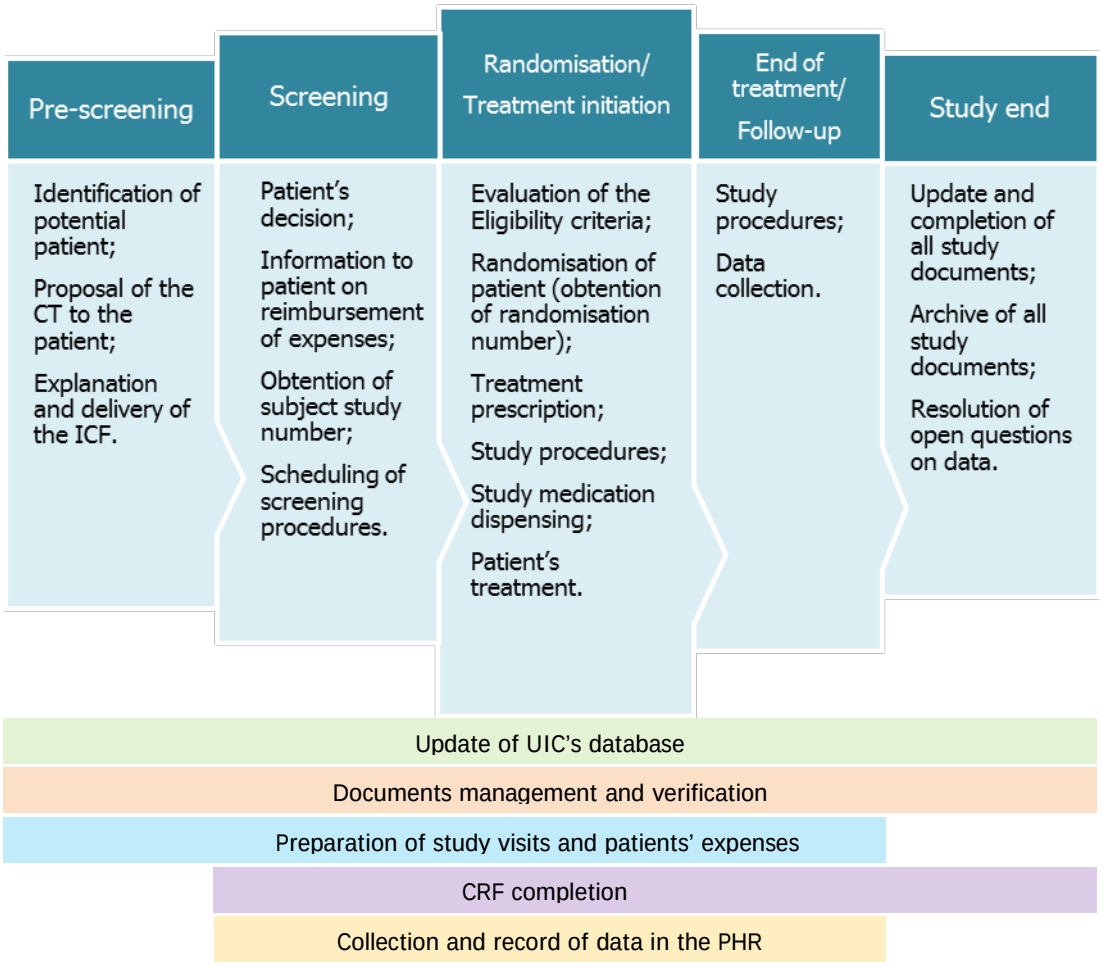


Table 7. Study Coordination Activities performed in different Clinical Trials

Activity / CT	*Study visits*[1]						*Other activities*			
	ICF	Screening	Randomisation	Treatment	End of Treatment	Follow-up	e-CRF	Monitoring visits	Documents management	Sample shipment
Urology										
C21004				x					x	
C21005				x					x	
FIRSTANA				x	x	x	x	x	x	
LATITUDE	x	x	x	x	x		x	x	x	
METEOR	x	x	x						x	
Lung										
1200.55	x	x	x	x			x		x	
Ideate	x	x	x	x	x	x	x	x	x	
LUX-Lung 8						x	x	x	x	
MK-3475-010	x	x	x	x					x	x
MuTAR				x		x	x	x	x	
Gynaecology										
ROSiA				x	x	x	x		x	
TRINOVA-1				x			x	x	x	
Intensive Care										
INHALE 2									x	
Paediatrics										
MK-0517-029			x	x	x	x	x	x	x	
Unspecified										
MK-0517-031	x	x	x	x	x	x	x		x	

[1] Study visits imply preparation of the visit, and scheduling of exams

As described in Figure 8 and Table 7, Study visits' preparation was an activity I performed systematically. The treatment preparation occurred more often, since this visit is more frequent (for example, screening and randomisation occur only one time). Regarding other activities, I performed documents management and e-CRF completion on a daily basis. Documents management was an activity transversal to all CTs, and to all stages of CTs' conduction, which I performed systematically. I also had the opportunity to assist monitoring visits of several studies, and to perform sample shipment of one CT.

2.2.2.1. Monitoring visits

Regarding monitoring visits, it is important to clarify that this is the moment when the Sponsor (in this case, the CRA delegated for the study) has access to the source documents. In these visits, the CRA's main role is to verify that the rights and well-being of the subjects are protected, that the reported data is complete and consistent with the source documents, without discrepancies, that there is compliance with the protocol, regulatory requirements and CGP, and identify action items for follow-up (35). The responsibilities of the CRA are described in (35). I had the opportunity to participate in monitoring visits. The SC's main role is to clarify the CRA, regarding the reported data, and to meet the action items identified in the monitoring visit. When necessary, the Investigator(s) should also be present.

Before the scheduled visit, I would prepare and organise all dossiers (Patient's File, PHRs, Investigator's Site File), to check if there was the need of archiving new documents or ask for updates of missing or inconsistent data. If so, I would note the aspects that needed the Investigator's amendment or clarification, so that the data could be updated in the monitoring visit. Also, I would verify if the e-CRF was up-to-date and proceed to its completion, and answer to queries when necessary. When I had any doubt related with the e-CRF completion, I would clarify with the CRA during the visit. I consider that the monitoring visits are a common effort to ensure that all documentation is accurate, and to meet the protocol requirements and data reporting issues.

2.2.2.2. Patient's visits

During my traineeship, I had the opportunity to be present in study visits required per protocol, in the Pathology Clinics of Urology and Lung and in the CT MK0517-031 (conducted in several clinics).

In these visits, the Investigator evaluates the patient's physical and clinical condition, and records the data, usually ECOG, physical exam, concomitant medication, evaluation

of laboratory results and signs and symptoms according to the “Common Terminology Criteria for Adverse Events” code, and RECIST evaluation when imaging is available. There are other requirements of data to be recorded and reported, that vary according to the type of study visit: Screening, Randomisation, Treatment, End of Treatment, and Follow-up.

UIC has a database with the list of potential patients and patients included in each CT. When the Investigator signals the patient, I update this database with the patient’s data. When the patient enters the screening, randomisation, treatment phase, follow-up, or end of study, I update the patient’s status in the database.

The next sections expose the study coordination activities to be performed when assisting to visits, but also the activities performed before and after the visits, and therefore likewise respective to the Pathology Clinics of Gynaecology and Paediatrics.

2.2.2.3. Pre-screening (Informed Consent Form)

When an Investigator signals a potential patient for a CT, he/she contacts the SC, so that she can be prepared to provide an ICF to the Investigator on the scheduled date, as well as the checklist of Inclusion/Exclusion Criteria.

In the pre-screening visit, the Investigator explains the CT to the patient and study procedures, and clarifies the patient’s doubts, emphasising that the patient may withdraw consent at any time. Training in GCP is very important while the ICF is being explained, so that the Investigator does not influence the patient’s decision. The patient should take the ICF home and make a thoughtful decision. Another visit is scheduled for any clarifications, and eventual inclusion in the CT. After signing the ICF(s), if the study protocol allows and the patient agrees, the screening visit can be performed in this same visit.

As a SC trainee, I ensured the data was appropriately recorded in the PHR, since it is required that the delivery of an ICF is recorded, and assisted the SC in the schedule of the patient’s screening exams. The data to be recorded is the identification of the current version of the ICF(s) and date, and whether the patient signed or not the ICF(s)—or the date when the patient has an appointment to provide his/her decision. I also verified if all ICF fields were filled by the patient and the Investigator, and provided a copy to the patient. After that, the SC would inform the patient about the expenses reimbursement and the screening exams foreseen schedule.

In some CTs, there are two separate ICFs (or even more) for the patient to sign. The general ICF is mandatory for the patient to sign, in order to participate in the CT. There are also other types of ICF, which are optional: Pharmacogenetics and/or pharmacogenomics ICF; Biological samples repository ICF; Future Biomedical Research ICF. If the patient wants to participate in the optional study, he/she has to perform additional biological tests or provide his/her data. Regarding the Future Biomedical Research, I had the opportunity to perform an online training on the matter and receive a certificate. This was important in order to know how to track these ICFs and record the patients' participation in the e-CRF, as well as being aware of what are the procedures to be done if a patient withdraws the consent anytime during or after the study.

2.2.2.4. Screening

Right after the patient gives his/her consent, the SC registers the patient in the IVRS/IWRS system, and obtains the patient's screening number, which identifies the patient in the study. A screening confirmation is obtained by fax, e-mail, or in the IWRS system. I have assisted to these steps, and learned how I should proceed. For example, some IWRS systems ask a small number of questions in order to screen the patient. These questions may be related to the eligibility criteria of the CT, and the SC may not be aware of the answer. Thus, the SC contacts the Investigator, in order to obtain an answer and proceed with the screening. This information should be recorded in the patient's PHR.

After obtaining the screening confirmation, the exams can be scheduled. The Investigator also has to record the physical and clinical evaluations, and record other required data, such as demographics, medical history and diagnosis, as well as the aforementioned data usually recorded in all study visits. I consulted the protocol, to ensure all exams were scheduled within the window timeline required by protocol, and its results available on time. Then, the patient would be informed of the screening schedule.

- **Sample shipment**

In protocols requiring tumour samples shipment to a central laboratory, I wrote a letter to the Pathological Anatomy Service of IPO-Porto, requesting the solid tumour sample of the patient. Together with the letter with the patient's information, I sent a previous histological report that might be available, for their orientation, and the shipping form if there was any information I could not gather myself.

After that, I received the sample and the complete form, and packaged the kit according to the shipping manual instructions of that specific protocol. Then, the SC

contacted the courier for scheduling the sample collection, and registered the reference number. Until this step, I acquired knowledge about the procedures concerning sample shipping at UIC. Then, I gathered the copy of the form and sent it by e-mail to the required address, with the expected information. I then archived the documents used in this activity in the Patient's File. The blood samples shipment is done by the study nurse.

2.2.2.5. Randomisation/Treatment initiation

After the screening visit, and before the patient's randomisation/treatment initiation, the Investigator evaluates the eligibility criteria: inclusion criteria and exclusion criteria. For this, the Investigator evaluates the results of the patient's screening exams. There are other factors to consider. For example, the patient's inability to fill in a diary may be an exclusion criterion, as it can mean non-compliance to the protocol. The Investigator performs the usual physical and clinical evaluation and records the required data per protocol in the PHR. The Investigator then fills the eligibility criteria form. If the patient does not meet the criteria, it is considered a Screening Failure, and registered in the IVRS/IWRS system as a screening failure by the SC. If the patient meets the criteria, he/she is randomised in the IVRS/IWRS system by the SC, and the patient stays allocated to a treatment arm. The medication is assigned to the patient in the same system.

In some CTs, the Sponsor may require a Qualification Visit before the randomisation visit, to assess a number of eligibility criteria, and other issues that may apply. The step that follows randomisation is the dispensing of study medication, which is described in the following section. The randomisation is done in the CTs with that design. When the study design does not require randomisation, this step is not done, and this visit is considered the study treatment iniation.

2.2.2.6. Treatment

The patient has study visits according to the schedule defined in the protocol, to evaluate his/her status and receive or discontinue the treatment. I prepare these visits according to the description provided in section 2.2.1.3. During the visit, the Investigator contacts the SC to assign the study treatment. The visit is registered in the IVRS/IWRS system, and the medication is dispensed. When applicable, the treatment batch number will be delivered. After that, the SC contacts the Investigator, to transmit the batch/box number.

The Investigator prescribes the medication using the prescription sheet specific for the CT, which was sent in the preparation of the study visit. Then, the operational assistant

brings a copy of the prescription to UIC. I write a letter, stating that the patient has been assigned the medication, and send it to the pharmacy by fax, with the prescription copy and the IVRS/IWRS confirmation attached. These documents and the fax confirmation are then archived in the Patient's File. If the patient is discontinuing the treatment, that information is registered in the PHR, and the medication is not assigned. Instead, an End of Treatment visit is scheduled according to the protocol window.

When the medication is oral, the Operational Assistant gathers the assigned medication from the Pharmacy, delivers it to the patient, and receives the medication left from the previous treatment cycle (and the medication diary, if applicable). This procedure is registered by the CTA. The patient takes home a medication diary, if required per protocol, and returns it filled in, in the next scheduled visit.

When the study medication is intravenous, it is administered in Day Care Hospital, by the study nurse, whom registers the procedure in the CT worksheets sent in the preparation of the PHR.

After the study visits, I archive the documents and fill the CRFs, with the supervision of the SC, as explained in section 2.2.1.7.

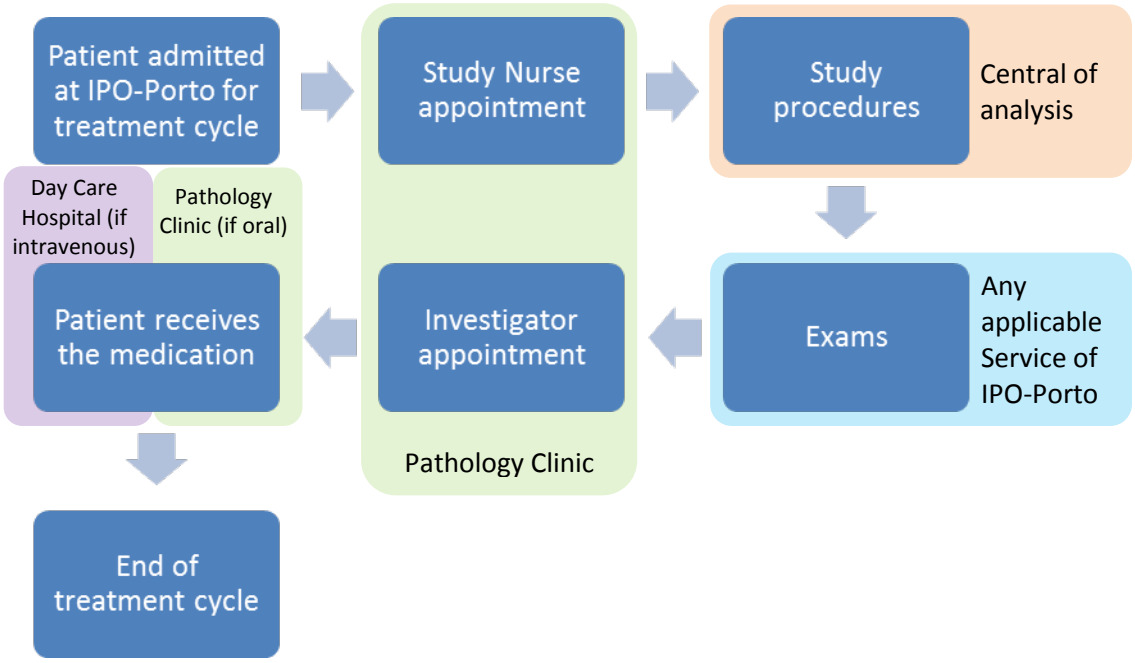
As my traineeship evolved, I understood the patient's treatment circuit within IPO-Porto during his/her visit:

First of all, the patient goes to the Pathology Clinic, and has a Nurse appointment, where the Study Nurse measures the patient's vital signs, and delivers the CT questionnaires if applicable (in some Pathology Clinics, this step may not occur, or be performed immediately before the Investigator's evaluation). Then, the patient goes to the central of analysis at IPO-Porto, where the Study Nurse performs the study procedures regarding biological sampling, for the local laboratory and/or the central laboratory (when and if applicable). If there are any other procedures to be performed at IPO-Porto before the Investigator's evaluation, the patient proceeds to the next service (for example cardiology service to perform an ECG, or nuclear medicine to perform a bone scan). After that, the patient has his/her appointment with the Investigator, at the Pathology Clinic. This is when the Investigator evaluates the results of the blood tests and other exams, to assess the patient's condition.

If the patient proceeds the treatment cycle, he/she receives the medication, after it has been assigned by the SC and dispensed by the Pharmacy: if it is oral medication, the patient receives the kit from the UIC's operational assistant; if the medication is

intravenous, the patient goes to the Day Care Hospital, and is administered the medication by the study nurse. The visit is then complete. If the patient does not meet the criteria to continue the treatment per protocol or by investigator decision, another visit is scheduled, for new assessment of the patient's condition, and a medical intervention may be performed if necessary. The circuit of a patient enrolled in CTs at IPO-Porto is represented in Figure 9 (it should be noted that the study nurse appointment may occur only after the study procedures, before the Investigator appointment).

Figure 9. CT Patient's treatment circuit within IPO-Porto



2.2.2.7. End of treatment

When a patient ends or discontinues the treatment, he/she has a study visit where the Investigator records the data required per protocol and evaluates the patient's status and next course of treatment if applicable. The patient is discontinued in the IVRS/IWRS system by the SC, and the reason is provided. The IVRS/IWRS confirmation is archived in the Patient's File. The reasons for ending the treatment may be completion of treatment, progression of disease, unacceptable toxicity, AE, non-compliance to protocol, Investigator decision, pregnancy or withdrawal of consent. Regarding my experience, I verified the end of treatment due to progression of disease (for example in lung cancer), completion of treatment (for example in ovarian cancer) and decision of the patient to end

the treatment due to its long duration, and with the support of the Investigator (for example in prostate cancer).

When the patient ends the treatment he/she enters the follow-up phase, to be followed for toxicity, progression, or survival.

The data of all CT visits is recorded in the e-CRF.

In the scope of my traineeship, these were the activities in which I was engaged most of the time, with emphasis on the Pathology Clinics of Lung, Urology, Gynaecology, and Paediatrics.

3. Discussion

3.1. STUDY COORDINATION EXPERIENCE

Working in a clinical research site with a team with 8 years of experience was a challenging opportunity. Every professional had well defined roles and tasks within IPO-Porto. However, my traineeship, overlapped with the entry of CTAs to the team. Thus, I accompanied the evolution and redefinition of tasks that they would be responsible for. This was a challenge because, as a trainee, I needed to learn the functioning of the institution and familiarise with some processes that were being performed by the CTAs. My strategy was to perform myself those tasks, or to understand how the tasks I could not do often are done. An example is the telephonic contact with the patients, and with the services/laboratories responsible for scheduling exams. I performed those tasks effortlessly, but not in a constant basis, what could have been beneficial for understanding the communications flow within IPO-Porto. However, I do not consider this a limitation for my professional activity, since it is a simple task.

Regarding my role within UIC, I feel part of the team, and have a close relation to them. The biggest challenge occurred during the period of time in which I did not have an assigned supervisor (officially). At first, I was not sure whether I could perform some activities, and who would be responsible for assigning those tasks. However, I would always clarify any doubt that I had, and perform every task that I was given an opportunity. As I got confident with my role within UIC, I would ask for a chance to fulfil any training gaps, and there was an effort to respond to all of them, which I am grateful for.

Concerning the training and the tasks I performed at UIC, I identified some issues that I would like to address. For example, regarding the patient's clinical data, the documents are recorded in an electronic database at IPO-Porto. Thus, in order to keep the Patient's File complete, I had to print the patient's electronic data, such as laboratory reports and the patient's diary. Therefore, data would be available for monitoring visits and CRF completion. There have been some concerns appointed by the Sponsors regarding the validity of the electronic PHR. The CRAs do not have access to this system within IPO-Porto, since it is not possible to restrict their access for each CT. UIC's strategy was to print the clinical diary and ask for the Investigator to sign the patient diary and exams, validating the data. This is not easy to implement, since Investigators attend many

patients per day, and have to be quick between appointments, what may pose a difficulty to print the diary and sign it right away.

Considering the clinical research area, where there is the component of uncertainty, the patient should always be in first place. For this matter, at UIC, SCs always try to help in any way they can. For example, reimbursement should be done as quickly as possible, since patients that have financial difficulties should not feel obligated to refuse or withdraw consent due to this reason. To address this issue, a new procedure is being thought-out (12): IPO-Porto reimburses the patient, and then the Sponsor reimburses IPO-Porto. This reduces the time the patient dispends while waiting for reimbursement. Therefore, the patient can participate in the CT even if he/she has financial difficulties.

On the topic of the subject's treatment, there were three different types in the studies I was enrolled in: oral treatment; intravenous treatment on Day Care Hospital; and intravenous treatment with hospitalization. Considering the SC's perspective, oral medication is the easiest treatment to report in the e-CRFs and the treatment that is more comfortable for the patient. However, intravenous medication requires more study procedures for the administration of the drug, and sometimes patients may develop hypersensitivity reactions. Thus, CTs that involve intravenous treatment, are usually more challenging to conduct and less comfortable for the patient, especially when the treatment involves hospitalization. A CT that is an example of treatment with hospitalization is the one conducted in paediatric patients. This CT's data was particularly tough to report, since in hospitalization, the clinical diary is updated several times a day, and the information may be disperse and difficult to summarise, or the required data may be difficult to identify. Thus, the strategy I developed was to compile the information that was already reported, and compare it with the data that was being reported, in order to reduce discrepancies or repetition of data. If needed, a clarification could be requested to the responsible for that data record. This increased my organisation for that CT and the following activities I performed.

Regarding the training I acquired at IPO-Porto, there are some activities in which I could not participate in, due to the organisation and specific rules of the institution. As explained in specific sections of the Regulatory Affairs (sections 2.1.1.2 and 2.1.1.3), I did not participate in these activities because they are not performed by SCs at UIC, even though I had a global idea of the general activities.

Concerning the specific training, I did not have the opportunity to participate in close-out visits, since they are only occur once. A close-out visit occurs when the CT ends (no

patients left to be followed) or due to early termination of CT. This visit has the objectives of solving open questions on data (e-CRF, queries, SAE report, clarifications, and notes-to-file); ensuring all documents are up-to-date, complete, and archived; handling the remaining IMP and trial materials; and ensuring fee payments are correct and complete (58). When a CT ends, it has to be ensured that all documents are archived and can be consulted if necessary.

In addition, I did not have the opportunity to participate in Investigators Meetings. The Investigators Meeting is attended by all the Investigators participating in the CT, and by SCs and or Study Nurses—as a trainee, I could not participate. This meeting provides training in the IMP and the CT, and is conducted before the CT begins. Its objectives are to ensure all staff receives the same information; provide specific training in the therapeutic area, the protocol and CRF; enable the staff to have an open discussion concerning the CT challenges and best practices; and provides a better view of all work and staff involved in the CT (59).

Regarding Quality Management in Study Coordination, a SC has to ensure that all information is recorded and accurate, and that there is compliance with the protocol. For this matter, and whenever data is not properly recorded in the PHR, I would list the missing/inconsistent data and ask the responsible to correct or record the data in the PHR. Furthermore, quality is maintained through the performance of periodic internal audits. However, I did not have the opportunity to participate in one of those audits, due to the UIC's organisation. When there is an audit, and depending on the findings, a Corrective Action and Preventive Action Plan may be implemented.

Concerning the construction of documents at UIC, I have been given the opportunity to construct standard operating procedures for the pre-screening, screening, randomisation, and study termination, at IPO-Porto. These documents were constructed in the last month of my traineeship (June). These tasks allowed me to practice my medical writing skills and to contribute to the improvement of quality in clinical research at UIC.

UIC has a very well organised and defined structure. During my traineeship, I identified several types of professional relationships in a SC's daily routine.

The SC's relationship with the patient is very important, as aforementioned, since they may have significant doubts, and the SC may help. Furthermore, Oncology patients are usually overcoming a difficult phase of their lives. Thus, the SC should have the proper sensitivity while contacting with the patient.

Working with several Pathology Clinics allowed me to learn from different professionals and create my own perspective of the professional I aspire to be. A good professional relationship between the SC and the CT team, especially with the Investigators, strongly contributes for the success of a CT.

From my experience, working with Urology CTs is rewarding, in the sense that the team is very motivated and organised, with strong support from the study nurses (who also complete CRFs for some CTs of this Pathology Clinic), and the tasks that were assigned to each member of the team were fulfilled in a cooperative manner. Support from the study nurses' team is very important for the success of the CT and accompanying of the patient in the beginning of each treatment cycle. The study nurse gives any needed information and clarifies patients' doubts, before the procedures. Since the SC has several CTs to attend to, and may not be present when the patient arrives to the institution (because the patients may arrive before the SC's working hours), the Study Nurses' support is a good advantage in this Pathology Clinic.

Lung CTs were an opportunity for me to learn and grow as a professional. I learned a lot from these CTs, since the Pathology Clinic of Lung asked for the SC's presence more often. Lung CTs demand more procedures than other CTs, what can be challenging. Thus, I had the opportunity to go to this clinic frequently, and observe its functioning. The Pathology Clinic of Lung is different from the Urology Clinic, essentially in the support from the Study Nurses' team. Thus, the SC has to give more support to the CT team, and the Investigators do not have the same support as in the Pathology Clinic of Lung. Also, to improve the Pathology Clinic's performance and strengthen the staff's engagement, a strategy that is being developed is the compilation of all Lung CTs' criteria and summaries of the protocol to support the Investigators.

In the context of working with professionals from another institution, I acknowledged that the relationship between the SC and the CRA is very important in order to achieve a supportive teamwork, for example concerning the e-CRF completion and when there are any doubts or a strict deadline to meet (such as an interim analysis). It is important to focus that, although they are professionals from different institutions, the SC and the CRA have to work together to comply with the protocol and GCP.

In addition, an issue that was part of most of my working days was communication with Data Managers/Medical Managers, through e-CRF completion. While completing e-CRFs and answering to queries, I would sometimes describe the interaction between the SC and data manager as a "Ping-Pong game". In some situations, this interaction may be

difficult, since the Data Manager/Medical Manager does not have access to source documents. If there is any discrepancy, the Data Manager/Medical Manager generates a query that is answered by the SC. Sometimes, the answer may not be satisfactory, and the query has to be clarified. It is important to provide all information clearly and concisely, by both professionals, to solve the query as soon as possible.

In relation to all this thoughts, I consider that cooperation and team spirit are determinant factors for the success of any multidisciplinary team that wants to achieve a common goal—especially in a healthcare institution.

3.1.1. Special and vulnerable populations specificities

As stated in section 1.3.4, special/vulnerable populations participate in Oncology CTs, and require distinctive attention. Since I was enrolled in Oncology CTs, I dealt with representatives of such populations (children, in Paediatrics; elderly in Lung and Urology; vulnerable subjects, in Intensive Care).

I identified some potential difficulties related with special populations, regarding ICFs signature. For example, geriatric patients may have difficulties writing their name in the ICFs. Thus, it has to be written in the PHR that, although the patient was able to sign the ICFs, he/she was not able to write the full name or the name with capital letter. Having an accompanying person during this visit is important, to help the patient understanding the document. Furthermore, elderly or non-instructed patients may have some concerns about the CT, regarding the study procedures and the need to do additional exams that they would not perform according to the clinical practice. Other issues may be related with the Investigator opinion. This is, the patient may have the need to ask directly if the Investigator considers the IMP a better option. According to GCP, the Investigator should not influence the patient's decision. For this reason, the Investigator should clarify some considerations about the CT in general, and clarify specific doubts related with the IMP and the need to perform additional tests and doctor appointments, but not give a personal opinion.

Regarding paediatric patients, they are not legally able to provide consent. The people responsible for their participation in a CT are their parents/legal guardian (34, 60). Thus, the ICF is signed by the responsible person. The Investigator should explain the CT to the minor in terms he/she can understand, and obtain his/her assent, when possible (34, 60). Concerning the CT MK0517-029, patients of appropriate intellectual maturity and able to

write their names, should sign the written assent form, which is a separate document, if they agree to participate in the CT.

Patients unable to give consent are considered vulnerable, since they depend on other person's decision (35). As an example, the INHALE 2 CT was specifically indicated to intubated and mechanically-ventilated patients with gram-negative pneumonia (56, 57). Thus, it was pointed out by the PI that obtaining the patients' consent would be a significant difficulty, since they would be bedridden and debilitated. If the patient is unable to provide oral consent, the legally acceptable representative should be the one to decide if the patient participates in the study, and give his/her consent (35). If the patient is able to give his/her oral consent, an impartial witness should be present during the ICF discussion. The witness should sign and date the ICF, attesting that the patient has been explained the ICF and apparently understood its information (35). The witness also attests that the patient freely gave his/her consent (35). During the period of my traineeship, no patients were randomised for this CT, and I have not experienced this situation. In this CT, there was a screening failure at the centre, during the weekend. I was not able to attend this appointment, since UIC is closed at weekends.

3.2. TRENDS IN EUROPEAN AND PORTUGUESE CLINICAL TRIALS

The number of CTs in the European Union, dropped 25% between 2007 and 2011 (61). The Directive 2001/20/EC fostered the decline in clinical trial activity in the European Union, due to the R&D expenditure, CTs' feasibility, recruitment targets and non-harmonised rules for multinational CTs (61, 62). A new regulation on CTs has been published in May 2014 (63), in an attempt to facilitate the conduct of multinational CTs. The scope of the "Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC" encompasses all CTs conducted in the European Union (63).

The new regulation defines new considerations in what concerns the approval of CTs from each Member State: a single notification with the CT authorisation or refusal will be issued by the Member State (63). This may have consequences for the CT approval process in Portugal, since three approvals are needed to initiate a CT (INFARMED, CEIC and CNPD). This regulation will come into effect in 28 May 2016 (63), and may be a good contribute for the improvement of bottlenecks in the conduction of CTs. Initiatives such as

IMI2 (18) also reveal an effort of improving the sector and bring innovative developments to provide better healthcare to individuals.

Regarding CTs in Portugal, its number is still reduced (9). PricewaterhouseCoopers International Limited has published a report on CTs in Portugal, in 2013, that describes specific challenges of CTs' conduction in Portugal (9). According to the report, CTs' reputation is negative; clinical research is not considered strategic for national economy; there is a lack of "clinical research culture"; the investigators are not properly recognised for their work; a few number of healthcare units are alert for clinical research; and there is lack of academic knowledge on CTs.

In addition, the report identifies issues that have been recently addresses in the new aforementioned Portuguese legislation on CTs (37): the deadlines for CTs' approval have not been competitive until now; there has not existed specific regulation regarding CTs' disclosure; and a platform for CTs' disclosure was lacking. These particular issues have been addressed, as proposed by the report, by the new Portuguese CTs' legislation, which has established competitive dealines for CTs' approval (as presented in section 2.1.1.1); established considerations about CTs' disclosure, and the National Registry of CTs to allow public disclosure of the national clinical research.

With the changes in the Portuguese legislation, we have started to address the bottlenecks that are critical in Portugal. The aforementioned report on CTs in Portugal proposes strategies to aid this process, such as the development of an independent organisation dedicated to clinical research; a national health education and CTs' disclosure strategy; and incentives to the inclusion of clinical research in professional careers.

As an institution with a well-established clinical research unit, IPO-Porto has shown a sustained number of patients recruited to its CTs, what is an example of the Portuguese potential of increasing the number of CTs and increase the clinical research in Portugal. Hopefully, more improvements will be made in Portugal, in order to foster clinical research and bring more CTs to the country.

3.2.1. Transparency in Clinical Trials

A topic that I consider important, and that is now starting to be addressed more seriously, is the need for transparency in CTs. Society has gained awareness on the need of generating clear evidence that supports a medicinal product's added value. An example

of an initiative developed to increase the transparency through registries is the “AllTrials campaign” (64). This global campaign defends that the results of CTs should be available to doctors and regulators, so that they can make informed decisions about treatments. Thus, the aim of the campaign is to make all evidence about a given treatment available, even the ones with negative results, so that its risks can be better understood (64). As another example, the EMA has published a draft policy on publication and access to clinical-trial data, to be adopted by the Board in July 2014. The debate on transparency through registries is still on, and the companies, Sponsors, and all stakeholders have already started to decide whether to be in favour or against these initiatives.

4. Conclusions

The traineeship experience at UIC was very useful to link the knowledge acquired in the Bachelor's in Biomedical Sciences and Master's in Pharmaceutical Medicine degrees with the work marketplace. I could put the knowledge I already had in practice, and complement it with a new perspective—on-the-job. Particularly, I solidified and/or remembered the knowledge in anatomy, GCP, clinical drug development and the drug life cycle, medicines regulation, psychology of communication, and ethics in clinical research.

Regarding specific activities, the development of Standard Operating Procedures and the medical writing skills I acquired, both during the academic training, were very useful for the development of Procedures for pre-screening, screening, randomisation/treatment initiation and study termination, at IPO-Porto. Besides, the Problem Based Learning method used in the Bachelor's degree, and the solid critical thinking skills I acquired from my academic background strongly contributed for the accomplishment of several activities during my traineeship. In addition, the participation in a study developed by the Clinical Research Office of the Health Sciences Department allowed me to have an idea of the patients' opinions and perceptions of clinical research, before starting the traineeship. This was helpful to understand the patients' needs, in terms of information and the level of detail and literacy that should be used while communication with each patient.

During the traineeship, I understood the SC's role in CTs conduction: It is a crucial role, functioning as a contact point between the Investigators, CT team, and the Sponsor. The SC has an active role, particularly in ensuring compliance with the protocol and GCP, problem solving, and keeping an appropriate record of data related with the CT, what can be very challenging. When I understood the study coordination reality, I acknowledged that the SC's role in CTs conduction may be determinant to its success. I also understood that at IPO-Porto, Study Coordination is restricted to the CT conduction after its approval, since this is a well organised study site, and UIC has well defined roles for each professional, due to its sustained growth since 2006. However, usually, Study Coordinators also cumulates regulatory affairs activities. I also would like to contribute to the activities that occur before and after CT conduction in a research site, to complete my experience.

The SC's day is never a routine: there are always new issues to address or follow-up, and many unforeseen issues and interruptions may occur. Thus, completing all tasks that were expected for the day may be difficult and requires strong time management skills

and focus. I had to find time to solve any problems that may occur, or urgent situations, such as an SAE to report. The priorities for the day may change, and a SC needs a good ability to make quick decisions and sound prioritisation, as well as strong communication skills.

As my traineeship evolved, I engaged more activities and responsibilities, which helped me to grow and develop communication skills and ability to focus. I verified that meeting the team and professionals allowed me to gain trust and participate more actively in discussions and give my opinion. Feeling part of the team helped a lot, and I can say that this experience will, for sure, help my future professional relationships.

During this traineeship, I was able to meet my primary objectives, regarding study coordination skills, and the reinforcement of my background knowledge, both from the BSc and MSc. The opportunity to participate in the coordination of 15 CTs in different areas of Oncology was a great approach to train a broad range of the study coordination activities. Being part of a team such as UIC permitted me to have a perspective of the working environment and understand the functioning of an organised and recognised clinical research centre.

Regarding the secondary objectives, I met most of the challenges. However, many of the Study Coordination activities I performed were observational, and some of them on-the-job. For example, I was present during several patients' study visits, but did not interact directly with them, and interacted with Investigators a few number of times. Although this was very useful to understand the communications' flow in a clinical research centre and to improve my communicational skills, it could have been beneficial to have the experience of speaking directly to the patients and explain the procedures or clarify any doubts. However, since I was performing other study coordination activities, it would have been difficult to be prepared to this situation without previous study and preparation, and this was not possible due to the organisation of UIC. Due to these visits to clinics, I understood the route of the PHR of the CTs' patients, which was a secondary objective. In addition, the development of internal procedures at IPO-Porto allowed me to understand its relevance for the quality of a clinical research centre. I acknowledged that quality assurance and GCP compliance are areas of personal interest for me, in which I would like to contribute to, more actively, in the future. I also would like to be involved in the conduction and/or preparation of an audit, to complement my training. I acknowledged that I would like to continue contributing for the quality of clinical research, as a professional of CTs.

5. References

1. PharmaTrain. Diploma Courses and Master Programmes. 2013 [cited 2014 April]; Available from: http://www.pharmatrain.eu/diploma/index.php.
2. IPO-Porto. Missão, Valores e Objetivos. [cited 2014 April]; Available from: http://ipoporto.pt/sobre/missao-valores-e-objetivos/.
3. IPO-Porto. História. [cited 2014 April]; Available from: http://ipoporto.pt/sobre/historia/.
4. Instituto Português de Oncologia e Esperança do Porto – Jornal 2 RTP2. IPO-Porto; 2014 [cited 2014 April]; Available from: http://ipoporto.pt/artigo-imprensa/instituto-portugues-de-oncologia-e-esperanca-do-porto-jornal-2-rtp2/.
5. IPO-Porto. Unidade de Investigação Clínica. [cited 2014 April]; Available from: http://ipoporto.pt/ensino-investigacao/unidade-de-investigacao-clinica-2/.
6. IPO-Porto. Research Center. [cited 2014 April]; Available from: https://sites.google.com/site/ipoportoresearchcenter/Homepage.
7. IPO-Porto. Centro de Investigação. [cited 2014 April]; Available from: http://ipoporto.pt/ensino-investigacao/centro-de-investigacao/.
8. Unidade de Investigação Clínica. Regulamento Interno da Unidade de Investigação Clínica. 2013:20 p.
9. PricewaterhouseCoopers International Limited. Ensaios clínicos em Portugal. 2013.
10. IPO-Porto. Clinical Research Unit. [cited 2014 April]; Available from: https://sites.google.com/site/ipoportoresearchcenter/researchgroups/clinicalresearch.
11. Smith CG, O'Donnell JT, editors. The Process of New Drug Discovery and Development. 2nd ed: Informer Healthcare; 2006.
12. Ferreira J. Operational Manager and Study Coordinator. 2014. Personal Communication.
13. Maia J. Good Clinical Practice and Quality Manager. 2014. Personal Communication.
14. Correia M. Internship Report in Clinical Studies Coordination at IPO-Porto [Report]: Universidade de Aveiro; 2013.
15. Número de doentes recrutados no IPO-Porto entre 2010 e 2013. [Unpublished data]. In press 2014.
16. EFPIA. The Pharmaceutical Industry in Figures. 2010.
17. EFPIA. The Pharmaceutical Industry in Figures. 2013.
18. IMI2. The right prevention and treatment for the right patient at the right time - Strategic Research Agenda for Innovative Medicines Initiative 2. 2014.
19. IMI. The Innovative Medicines Initiative (IMI) Scientific Research Agenda Revision. 2011.
20. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nature reviews Drug discovery. 2004;3(8):711-5. Epub 2004/08/03.
21. IMI. The Innovative Medicines Initiative (IMI) Strategic Research Agenda. 2008.
22. HHS. Critical Path Opportunities Report. In: FDA, editor. 2006.
23. PricewaterhouseCoopers. Pharma 2020: The vision. 2007.
24. The Textbook of Pharmaceutical Medicine. 6 ed: Blackwell Publishing Ltd; 2009.
25. ICH. E8 - General Considerations for Clinical Trials 1997.

26. Moreno L, Pearson AD. How can attrition rates be reduced in cancer drug discovery? Expert opinion on drug discovery. 2013;8(4):363-8. Epub 2013/02/05.
27. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403. Epub 2013/03/15.
28. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2013. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24(3):792-800. Epub 2013/02/14.
29. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2014. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014. Epub 2014/04/25.
30. Radtke S. Challenges in Oncology Clinical Trials at the Site Level. Journal of Clinical Research Best Practices. 2012;8(9):4.
31. ORACLE. Getting the Most Out of Your Oncology Clinical Trial: A Conversation with Ashok Bhat. ORACLE; 2011. p. 1-2.
32. IMI. IMI2 Strategic Research Agenda - The right prevention and treatment for the right patient at the right time. 2013.
33. ICH. E7 - Studies in Support of Special Populations: Geriatrics. 1993.
34. ICH. E11 - Clinical Investigations of Medicinal Products in the Pediatric Population. 2000.
35. ICH. E6 - Guideline for Good Clinical Practice. 1996.
36. Clínica de Pediatria. IPO-Porto; [cited 2014 May]; Available from: http://ipoporto.pt/clinica/hospital-de-dia-pediatria/.
37. Lei n.º 21/2014 de 16 de abril — Aprova a lei da investigação clínica, 1.ª série - N.º 75 (2014).
38. Idenix Clinical Investigator Feasibility Questionnaire. Idenix Pharmaceuticals; 2014 [cited 2014 May]; Available from: http://www.idenix.com/idenix-clinical-investigator-feasibility-questionnaire/.
39. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA : the journal of the American Medical Association. 2013;310(20):2191-4. Epub 2013/10/22.
40. Vision: ICH. Available from: www.ich.org/about/vision.html.
41. National Cancer Institute. Cancer Staging. [cited 2014 April]; Available from: http://www.cancer.gov/cancertopics/factsheet/detection/staging.
42. National Cancer Institute. Cancer Grade. [cited 2014 April]; Available from: http://www.cancer.gov/cancertopics/factsheet/detection/tumor-grade.
43. Eastern Coorperative Oncology Group. ECOG Performance Status. 2006 [cited 2014 April]; Available from: http://www.ecog.org/general/perf_stat.html.
44. National Cancer Institute. NCI Dictionary of Cancer Terms - Karnofsky Performance Status. [cited 2014 April]; Available from: http://www.cancer.gov/dictionary?cdrid=44156.
45. National Marrow Donor Program, The Medical College of Winsconsin. Forms Manual: Appendix L - Karnofsky/Lansky Performance Status. 2009. p. 1, 5.
46. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). National Institutes of Health; 2009.

47. RECIST - What is RECIST? : Parexel; 2014 [cited 2014 April]; Available from: http://www.recist.com.
48. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):229-30. Epub 2008/12/23.
49. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(7):1148; 58. Epub 2008/03/04.
50. Medidata Solutions Inc. Medidata Rave. 2014 [cited 2014 April]; Available from: http://www.mdsol.com/products/rave/overview.
51. InForm System Training. [cited 2014 April]; Available from: http://library.dcri.duke.edu/dtmi/InForm/02/02.htm.
52. Oracle Remote Data Capture. [cited 2014 April]; Available from: http://www.oracle.com/us/products/applications/health-sciences/e-clinical/remote-data-capture/index.html?ssSourceSiteId=opn.
53. Datatrak International Inc. About DATATRAK. [cited 2014 April]; Available from: http://www.datatrak.com/about-datatrak/.
54. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for Industry - Electronic Source Data in Clinical Investigations. 2013. p. 4-6.
55. Clinitec IVRS / IWRS. Clinitec Pty Ltd; [cited 2014 June]; Available from: http://www.clinitec.com.au/ivrs_iwrs.html
56. IPOP_Ensaios em Recrutamento e a Iniciar Brevemente. In: Dinis J, Maia J, editors. IPO-Porto2014.
57. EU Clinical Trials Register [database on the Internet]. European Medicines Agency,. 2014 [cited May 2014]. Available from: www.clinicaltrialsregister.eu/ctr-search/search.
58. KKS-Network. Standard Operating Procedure - Close out Visit 2011.
59. Hints & Tips for Clinical Research - Number 4 - Investigator Meetings. In: The Institute of Clinical Research, editor.
60. Lei nº 46/2004 de 19 de Agosto - Aprova o regime jurídico aplicável à realização de ensaios clínicos com medicamentos de uso humano, 195. Sect. 2.º - Definições (2004).
61. Proposal for a Clinical Trials Regulation - Questions and answers. Brussels: European Commission; 2012.
62. Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, (2012).
63. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 158/1 (2014).
64. All Trials Registered | All Results Reported. Available from: http://www.alltrials.net/blog/the-alltrials-campaign/.