Universidade de Aveiro Departamento de Ciências Médicas

2016

JOANA CRISTINA MENDES CRUZ DE SOUSA

TRAINING REPORT IN CLINICAL TRIALS COORDINATION AT BLUECLINICAL, LTD

RELATÓRIO DE ESTÁGIO EM COORDENAÇÃO DE ENSAIOS CLÍNICOS NA BLUECLINICAL, LTD

Universidade de Aveiro Departamento de Ciências Médicas

2016

JOANA CRISTINA MENDES CRUZ DE SOUSA

TRAINING REPORT IN CLINICAL TRIALS COORDINATION AT BLUECLINICAL, LTD

RELATÓRIO DE ESTÁGIO EM COORDENAÇÃO DE ENSAIOS CLÍNICOS NA BLUECLINICAL, LTD

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado do Departamento de Ciências Médicas da Universidade de Aveiro e da Dra. Lucília Penteado, *Clinical Research Manager* na Blueclinical Ltd.

“The capacity to learn is a gift;
The ability to learn is a skill;
The willingness to learn is a choice.”

Brian Herbert

o júri

presidente	Professor Doutor Nelson Fernando Pacheco da Rocha professor catedrático da Universidade de Aveiro
arguente	Professora Doutora Alexandra Isabel Cardador de Queirós professora coordenadora s/agregação da Universidade de Aveiro
orientador	Professor Doutor Bruno Miguel Alves Fernandes do Gago professor auxiliar convidado do Departamento de Ciências Médicas da Universidade de Aveiro

agradecimentos

Ao Professor Luís Almeida e ao Professor Bruno Gago, responsáveis pelo Mestrado em Biomedicina Farmacêutica, pela orientação e pelos conhecimentos transmitidos durante estes dois anos.

Ao Professor Luís Almeida, ao Professor Sérgio Simões e à Dra.Cristina Lopes, pela oportunidade de realizar o meu estágio curricular na Blueclinical.

Ao Professor Bruno Gago e à Dra. Lucília Penteado, pela pronta disponibilidade, orientação e revisão deste relatório.

A toda a equipa da Blueclinical, em especial à Vanessa Valente, por me terem acolhido.

A todos os meus amigos, sem exceção, agradeço a amizade e o incentivo.

Aos meus colegas de mestrado, pelos momentos de entusiasmo e aprendizagem partilhados em conjunto.

A todos os departamentos do Centro Hospitalar de Vila Nova de Gaia/Espinho com os quais colaborei.

Aos meus pais, sem os quais não teria sido possível concretizar esta etapa da minha vida.

palavras-chave

investigação clínica, coordenação de ensaios clínicos, ensaios clínicos, estudos observacionais, centro de investigação, Biomedicina Farmacêutica, Blueclinical

resumo

Este relatório descreve as atividades desenvolvidas como coordenadora de ensaios clínicos no âmbito do estágio curricular do Mestrado em Biomedicina Farmacêutica, lecionado na Universidade de Aveiro.

O estágio curricular decorreu no Centro Hospitalar de Vila Nova de Gaia/Espinho, no período compreendido entre 15 de setembro de 2015 e 15 de abril de 2016.

O relatório encontra-se estruturado em sete capítulos, sendo que no segundo capítulo são mencionados os objetivos do estágio, procedendo-se no capítulo seguinte à caracterização das instituições acolhedoras. Posteriormente, no capítulo quatro é apresentado o estado de arte do processo de investigação e desenvolvimento farmacêutico, incluindo a caraterização da situação atual dos ensaios clínicos em Portugal. As atividades realizadas no âmbito da coordenação de ensaios clínicos estão descritas no capítulo cinco. Nos últimos capítulos, analisa-se e procede-se à avaliação do estágio, sendo também mencionadas as estratégias adotadas para solucionar os problemas e dificuldades que foram surgindo.

Em suma, considero que o estágio curricular cumpriu a sua finalidade, ao possibilitar a aquisição de competências como coordenadora de investigação clínica.

keywords

clinical research, clinical research coordination, clinical trials, observational studies, clinical research centre, Pharmaceutical Medicine, Blueclinical

abstract

This report describes the activities performed as clinical research coordinator, during the internship of the Master in Pharmaceutical Medicine, at the University of Aveiro.

The curricular internship took place at Blueclinical – particularly at Centro Hospitalar de Vila Nova de Gaia/Espinho, from 15th September 2015 to 15th April 2016.

The report is divided into seven chapters. The training objectives are presented in the two chapter, and in the next chapter the host institutions are characterized. Then, in the four chapter it is presented the state-of-the-art of the pharmaceutical research and development process, including the current situation of the clinical trials in Portugal. The activities carried out under the scope of the clinical trials coordination are described in five four. In the last chapters, it is performed a critical analysis and the assessment of the internship, and are also mentioned the strategies adopted in order to solve the problems and difficulties that arose.

In conclusion, I consider that the internship fulfilled its purpose, providing the acquisition of skills as clinical research coordinator.

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

LIST OF ABBREVIATIONS

AB	Administration Board
CEIC	Comissão de Ética para a Investigação Clínica (National Ethics Committee for Clinical Research)
CES	Comissão de Ética para a Saúde
CHVNG/E	Centro Hospitalar de Vila Nova de Gaia/Espinho
CNPD	Comissão Nacional para a Proteção de Dados (The National Commission for Data Protection)
CPT	Critical Path Initiative
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRP	Clinical Research Partnership
CRO	Clinical Research Organization
CV	Curriculum Vitae
eCRF	Electronic Case Report Form
EMA	European Medicine Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIC	Gabinete de Investigação Clínica (Clinical Research Office)
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	Investigator Meeting
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde
ISF	Investigator Site File
IVRS/IWRS	Interactive Voice/Web Response System
MS	Member State
NME	New Molecular Entity
PI	Principal Investigator
POC	Proof-of-Concept

PRO	Patient-Reported Outcomes
R&D	Research and Development
SAE	Serious Adverse Event
SIV	Site Initiation Visit

1. INTRODUCTION

The present report describes the activities performed as Clinical Research Coordinator (CRC), in the scope of the internship of the Master in Pharmaceutical Medicine, at University of Aveiro.

This curricular internship was developed at Blueclinical – particularly at Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E), from 15th September 2015 to 15th April 2016. The activities were performed under supervision of Dra.Lucília Penteado, Clinical Research Manager at Blueclinical.

The internship is a key part of the academic path to complement the teaching-learning process. This practical experience allowed me to apply and to consolidate the scientific and theoretical knowledge learned during the Master. Moreover, it also allowed me to acquire and to develop competences/skills in professional environment as CRC. Nowadays, the role of CRC has been a growing importance considering the increase of complexity of the clinical trials and the tighter regulatory requirements. Furthermore, CRC is a link between the research subjects, the investigator and other site team members. CRC has a vital role at site to the execution of a successful clinical trial.

In this report, I will describe my work experience in the field of clinical research.

This report is divided into seven chapters, which comprises a) the identification of my training objectives and personal goals (chapter 2), b) the presentation of the host institutions, namely the history, the vision and the organisation (chapter 3) and c) the state of the art of the Pharmaceutical Research and Development process and the current situation of the clinical trials in Portugal (chapter 4). In the chapter 4, I also considered relevant to include an overview of the regulatory framework. The activities carried out during the internship are described in chapter 5, and in the subchapter 5.2, the specific activities performed as CRC are explained, since the beginning of a new trial or study to the closeout of the trial. In the last chapters 6 and 7, I will analyse my internship experience and I will discuss the outcomes of this trainee.

2. TRAINING OBJECTIVES

The internship was planned in order to achieve the following objectives:

- to develop skills as CRC;
- to identify the working procedures at clinical research site;
- to contribute to the improvement of the clinical research at CHVNG/E;
- to acquire knowledge of pathological aspects and treatment guidelines of several diseases;
- to apply learned concepts and skills to a practical setting;
- to recognise the multidisciplinary framework of the activities developed in the scope of the clinical research coordination;
- to manage time effectively;
- to improve communication and problem solving skills on-the-job training;
- to establish networking with peers, investigators and others professionals and institutions;
- personal and professional development.

3. OVERVIEW OF THE HOST INSTITUTION AND PARTNER HOSPITAL

This chapter presents a description of the host institution Blueclinical - Investigação e Desenvolvimento em Saúde, Ltd., its structure, activities and its role in promoting clinical research. Although, Blueclinical - Investigação e Desenvolvimento em Saúde, Ltd henceforth referred to as Blueclinical, was the host institution of my internship, my activities as CRC were performed at CHVNG/E. Therefore, I consider that it is also relevant to mention this institution in this chapter.

3.1. BLUECLINICAL

Blueclinical is a translational medicine company that was founded in May 2012 and is headquartered at Avenida Villagarcia de Arosa, Matosinhos – Porto. The aim of this company is to bring the projects of institutions, startups and established companies to clinical practice (1). To achieve this purpose, Blueclinical's activity is organized into three business units: Research and Development (R&D), Phase I and Clinical Research Partnership (CRP), which cover all the different phases of the drug discovery process (1). The public organogram outlines the internal structure of Blueclinical (figure 1).

BLUECLINICAL R&D

The mission of Blueclinical R&D is to establish partnerships with institutions and companies in the development of successful translational medicine projects (2). This business unit intends translating basic research findings into investigation in humans, and finally, into medical care (2). Blueclinical R&D unit provides a unique expertise and experience, namely in the definition of the development and the business plans. Their consulting services include:

a. preparing and implementing preclinical, clinical and regulatory plans for new medicines medical devices and other health products;

b. the definition of the target product profile and the definition of preclinical and regulatory plans;

c. preparing and supporting the process of obtaining scientific and regulatory advice from competent regulatory authorities;

d. placing and monitoring preclinical studies;

e. preparing the investigator's brochure and investigational medicinal product (IMP) dossier;

f. preparing and submitting the clinical trial application to the competent authorities and ethics authorities;

g. planning, conduction and reporting clinical pharmacology clinical trials (Phase I) in healthy subjects or patients; ´

h. planning, implementing, monitoring and reporting therapeutic clinical trials (Phase II to IV) or observational studies with medicines or medical devices (2).

Furthermore, Blueclinical R&D has interest into to participate in international consortia candidate to Horizon 2020 calls or to other funding agencies (2).

BLUECLINICAL PHASE I

Blueclinical Phase I is a clinical research unit, whose mission are conducted effective studies in healthy subjects and early stage studies in selected patients populations. This unit was founded on 12th July 2013. Its facilities are located at Hospital da Prelada, in Porto, with large benefits that include its location with easy accesses, an efficient logistic service and an accredited clinical laboratory. Phase I unit has modern, safety and comfort facilities, with 34 beds (3).

Phase I unit has a clinical and scientific team with long experience in diverse types of studies for the global market, both generics and innovative medicines, such as:

a. bioavailability/bioequivalence studies, to determine the similarity of different formulations of the same medicine, according to the requirements of the European Medicine Agency (EMA), Food and Drug Administration (FDA) and other regulatory authorities;

b. Phase I studies with innovative medicines;

c. drug-drug interactions studies;

d. food interactions trials to evaluate if medicines must be taken along with food or out of meals;

e. dosage form proportionality studies;

f. entry-into-Man trials;

g. studies with special populations (3).

All studies are conducted in compliance with international regulatory and ethical standards, after approval from the competent authorities, the National Ethics Committee for Clinical Research (*Comissão de Ética para a Investigação Clínica* – CEIC) and the National Committee of Data Protection (*Comissão de Nacional de Proteção de Dados* - CNPD).

Volunteers with an interest in participating in the above-mentioned trials can apply to Phase I email. Then, they are contacted by phone and inquired if they are interested and have availability to perform a screening visit, considering the trials that will be performed at Phase I facilities.

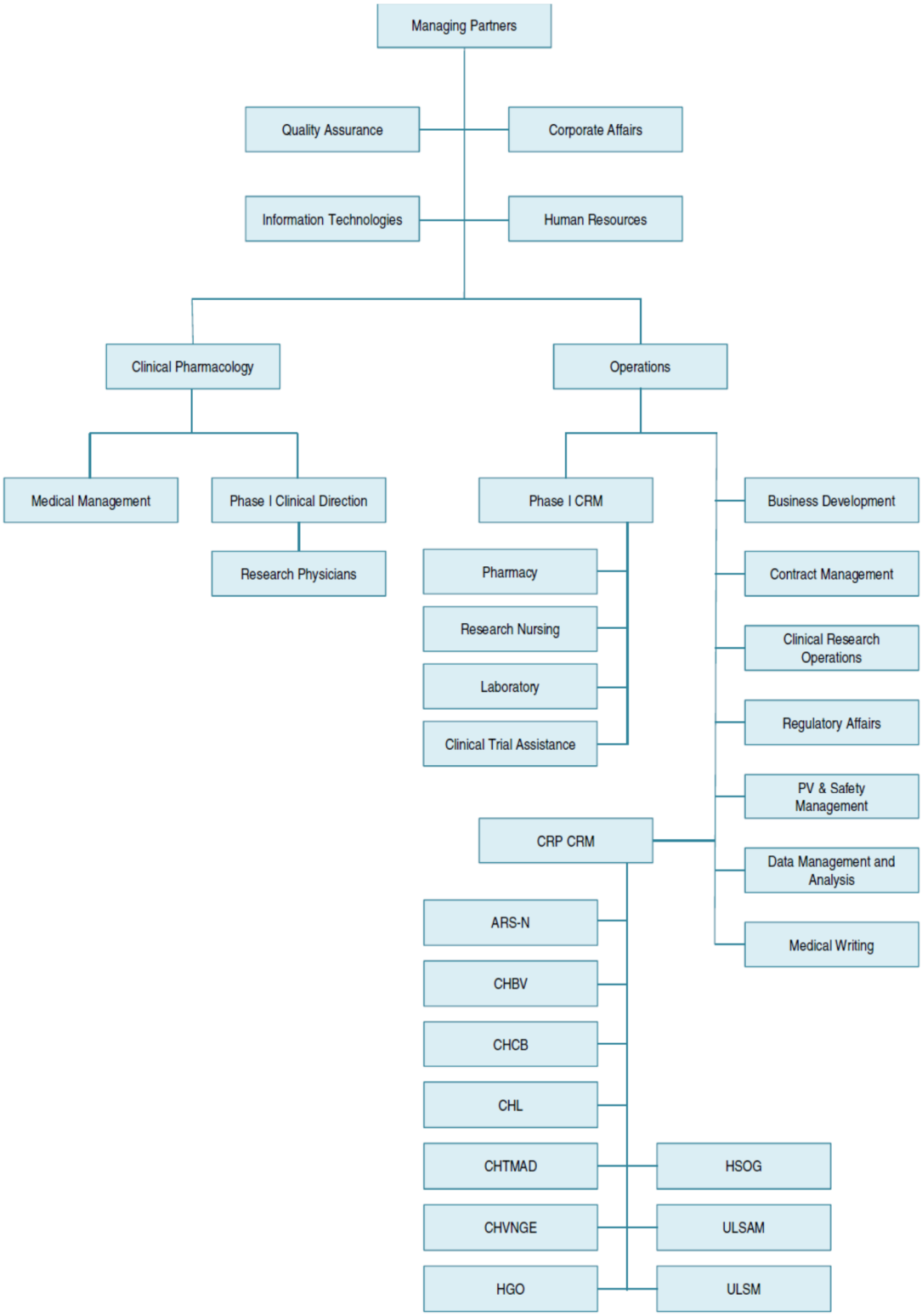

Figure 1 Public Blueclinical's organogram

ARS-N *Administração Regional de Saúde do Norte*; **CHBV** *Centro Hospitalar do Baixo Vouga, E.P.E.*; **CHCB** *Centro Hospitalar da Cova da Beira, E.P.E.*; **CHL** *Centro Hospitalar de Leiria, E.P.E.*; **CHTMAD** *Centro Hospitalar de Trás-os-Montes e Alto Douro, E.P.E.*; **CHVNGE** *Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E.*; **CRM** *Clinical Research Management*; **CRP** *Clinical Research Partnership*; **HGO** *Hospital Garcia de Orta, E.P.E.*; **HSOG** *Hospital Senhora da Oliveira Guimarães, E.P.E.*; **PV** *Pharmacovigilance*; **ULSAM** *Unidade Local de Saúde do Alto Minho, E.P.E.*; **ULSM** *Unidade Local de Saúde de Matosinhos, E.P.E.*.

BLUECLINICAL CRP

The mission of Blueclinical CRP is to support the activity of clinical research centres, promoting mutual growth, efficiency and excellence in clinical research. Blueclinical CRP is a network of hospitals and primary care centres. Approximately 5 million of the Portuguese population has access to these institutions (4).

The main reasons of the lack of the efficiency of clinical research are related with administrative or organizational factors. Thus, Blueclinical CRP through the creation of highly motivated and organized teams and efficient structure intends to deliver excellence in clinical research (4).

The research activity at the clinical sites supported by Blueclinical CRP is guided by three key principles: quality, training and support. The quality management system of this business unit assures that all clinical research activities are documented and performed through a standardized process. This management system pretends to maximize the efficiency of the processes and to assure full compliance with the legal and ethical requirements. Furthermore, training and qualification of each clinical research team member are stimulated and supported by CRCs at each centre (4).

CRCs provided by Blueclinical CRP are skilled, specialized and motivated professionals. They are committed to support the development of clinical research of high efficiency and quality, and to comply with all ethical and legal requirements (4).

Currently, Blueclinical CRP has partnership agreements contracts with the Administração Regional de Saúde do Norte, which comprehends the primary care units and nine hospitals, with different localizations. The following hospitals are supported by Blueclinical CRP in clinical research activities:

- Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E;
- Centro Hospitalar de Trás-os-Montes e Alto Douro, E.P.E;
- Centro Senhora de Oliveira, E.P.E;
- Centro Hospitalar do Baixo Vouga, E.P.E;
- Centro Hospitalar da Cova da Beira, E.P.E;

- Centro Hospitalar de Leiria, E.P.E;
- Hospital Garcia da Orta, E.P.E;
- Unidade Local de Saúde do Alto Minho, E.P.E;
- Unidade Local de Saúde de Matosinhos, E.P.E.

At each centre, the Administration Board (AB) designates a physician to coordinate the clinical research office.

3.2. CENTRO HOSPITALAR DE VILA NOVA DE GAIA/ESPINHO

CHVNG/E is a referenced centre of the north of the country. It offers a large range of healthcare services such as: a) a polyvalent emergency department for all age group, b) a medical and surgery care, c) a continuing care and a rehabilitation service, and also d) an ambulatory medical care of several medical specialties. Overall, CHVNG/E provides a wide range of health care services to 700 000 inhabitants, covering a geographic area that includes Vila Nova de Gaia, Espinho and Entre Douro e Vouga councils. It is also considered reference centre to all councils located at north of the country, above Vouga River (5).

This centre is divided in 3 units: a) unit I, previously known as Hospital Eduardo Santos Silva, located at Rua Conceição Fernandes, s/n – Vila Nova de Gaia; b) unit II, previously known as Hospital Distrital de Gaia, whose facilities are located at Rua Francisco Sá Carneiro, s/n – Vila Nova de Gaia; c) unit III, the old one Hospital Nossa Senhora da Ajuda, located at Rua 37, s/n – Espinho (6).

The clinical research office, designated as *Gabinete de Investigação Clínica (GIC)* is located at unit I, where it also located the main part of above-mentioned medical care services and the emergency room. In the hospital organization chart, GIC is integrated in the training, education and research department (figure 2) (7).

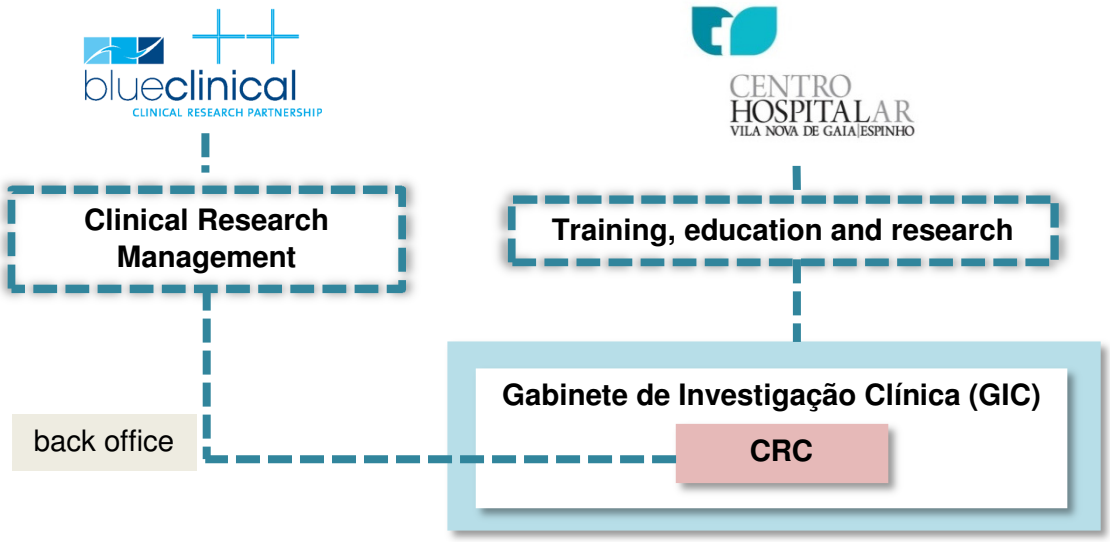

Figure 2 CRCs within Blueclinical's and CHVNG/E's organization

The CRCs integrate the Blueclinical CRP business unit, which is supervised by the Clinical Research Management. The back office gives supports to GIC. In the CHVNG/E's structure, CRCs are part of the support office of GIC.

4. STATE-OF-THE-ART

This chapter is intended to give an overview of the Pharmaceutical R&D process and the current situation of the clinical research, including the situation of the clinical trials in Portugal. Moreover, it is described the regulatory framework of the clinical trials.

4.1. CLINICAL RESEARCH

Clinical research plays a vital part in making progress towards better knowledge, understanding of human health and disease and the development of new, safe and effective treatments (8). The Regulation European Union (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, replacing the decade-old Directive 2001/20/EC – the Clinical Trials Directive, states that a clinical study means any investigation in relation to human intended:

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

b) to identify any adverse reactions to one or more medicinal products; or

c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products (9).

Two different categories of research can be established: clinical trials (using an IMPs, medical devices or can also include surgical, physical or psychotherapeutic procedures) and non-interventional trials (8).

Clinical trial means a clinical study which fulfils any of the following conditions:

a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice;

b) the decision to prescribe the IMPs is taken with the decision to include the subject in the clinical study; or

c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects (9).

In contrast to clinical trial, non-interventional studies are described as: “a study in the context of which knowledge from the treatment of persons with drugs in accordance with the instructions for use specified in their registration in analysed using epidemiological methods" (10, 11). These types of studies may be prospective and/or retrospective. In a prospective study, the investigator follows the impact of the exposure going forward in time and wait for the outcome of interest (13). In contrast, retrospective studies are conducted after the development of the outcomes of interest (10, 11).

Besides providing greater knowledge about the safety and effectiveness of treatment regimens with respect to the local standards of clinical care, non-interventional studies can also map risks in the real world (12). They are usually performed during phase IV of drug development.

4.2. BIO/PHARMACEUTICAL R&D PROCESS

Pharmaceutical R&D is defined as the process of discovering and introducing new drug products in the market (13).

Pharmaceutical and biotechnology companies are struggling to bring new molecular and biologic entities through R&D and to generate attractive returns on investment (14). Despite the number of new molecular and biologic entities in the R&D pipeline has been rising 7% annually, the average cost for pharmaceutical companies to bring a new molecular entity (NME) to market is also rising rapidly. The costs are now estimated to be approximately US$1.8 billion (14, 15). Therefore, R&D productivity has been declining over the years. The overall cohort internal rate of return has declined, from 10.1 per cent in 2010 to 5.5 per cent in 2014, but in 2014 for the first time, there has been a halt to the decline and even an upflit in R&D returns relative to 2013 (14-16). Several factors has contributed to make the pharmaceutical industry’s survival, at least in its current form, threatened, but the following stand out: a) a reduced R&D output in the form of successfully launched truly innovative NMEs, b) a diminishing market exclusivity for recently launched new medicines and c) the lost due to patent expirations for successful products (14, 15). Additionally, a range of environment issues also contributes to the

pressure under pharmaceutical industry, such as an increasingly cost-constrained healthcare systems and a more demanding regulatory requirements (15). The attrition rate remains high in drug development process, due the number of efficacy- and safety-related failures during clinical trials (15, 17). The main reasons to the failure during clinical trials are the lack of efficacy (25%), the clinical safety concerns (12%) and the toxicological findings in pre-clinical evaluation (20%) (18).

Regarding the long development timelines, despite the implementation of a wide variety of new practices and technologies intended to accelerate clinical development cycle times, the opposite has occurred (14). In 2010, the average clinical phase duration was 6.8 years, increasing 15% during the preceding decade (14).

Therefore, the R&D operating model, which served the drug development enterprise well during the past 50 years, is obsolete and no longer viable (14). New models of collaboration, including open innovation platforms, the integration of big data systems that leverage structured and unstructured electronic health information, modification of legacy processes, the adoption of adaptive clinical trial designs and more patient centric clinical trials, are all emerging approaches that hold promise in transforming R&D process and performance (14).

Besides that, two international initiatives, “Critical Path Initiative” (CPT) and “Innovative Medicines Initiative” (IMI) were developed to improve drug development and promote better medicines (18-20).

The purposes of CPT, developed by FDA in United States of America, are to increase efficiency and productivity of the R&D process, to create an innovative science and to reduce uncertainty, applying new scientific tools (19). The list identifies 76 tangible examples where new scientific discoveries – in fields such as genomics, imaging and informatics (the analysis of biological information using computers and statistical techniques) – can be applied during product development to improve the accuracy of tests that predict the safety and efficacy of potential medical products (21). This initiative outlined specific areas of Critical Path focus, including:

a. developing better evaluation tools such as biomarkers and new assays;

b. streamlining clinical trials by modernizing the clinical trial sciences to make trials safe and efficient;

c. harnessing bioinformatics (e.g. move from a paper-based to electronic environment for exchanging information and overseeing the safety of FDA-regulated products);

d. moving manufacturing into the 21st century using tools such as process analytic technology and nanotechnology;

e. developing products to address urgent public health needs, including improved antimicrobial testing, new animal models to test bioterrorism countermeasures and vaccine testing;

f. focusing on at-risk populations, such as paediatrics (19, 21).

The IMI is a public-private partnership developed by European Commission and the European Federation of Pharmaceutical Industries and Associations that aims to boost the development of new medicines by implementing new collaborative endeavours between biopharmaceutical companies, regulators, academy and patients (22). This initiative has 4 pillars: a) improvement the predictivity of drug safety evaluation, b) improvement the predictivity of efficacy evaluation, c) knowledge management through more information and data utilization and d) promotion of education to resolve training gaps (20, 22). There is already an IMI 2 initiative, developed to deliver the right treatment to the right patient at the right time for priority diseases, supporting the personalised medicine and prevention (20).

4.3. DRUG DEVELOPMENT PROCESS

The drug development process is typically divided into three major steps: discovery, preclinical development and clinical trials (23). Once a potential therapeutic drug or biologic has been discovered, the process of developing the therapeutic for a particular disease, begins with the preclinical development (24). This process encompasses the activities that link drug discovery in the laboratory to initiation of human clinical trials. Preclinical studies can be designed to a) identify a lead candidate from several hits; b) develop the best procedure for new drug scale-up; c) select the best formulation; d) determine the route, frequency, and duration of exposure; and e) ultimately support the intended clinical trial design (23). The transition from discovery to preclinical development is a continuum process, and results of preliminary pharmacology and toxicology testing

often contribute to lead drug candidate selection (23). It is estimated that 5000 to 10000 compounds are screened during the pre-discovery and discovery phases. Most of those compounds are eliminated, and about 250 are selected for the preclinical phase. To the preclinical tests, in average only 5 IMPs are selected and submitted as an investigational new drug (20). This application to regulatory authorities is mandatory before initiate clinical trials (23).

The clinical trials process of a study drug is conventionally divided into four phases, as described below:

a. **phase I (human pharmacology) -** these studies represent the first in-human exposure to the drug, and involve a small number of subjects, usually healthy non-patient volunteers (20-80). In some circumstances, the subjects involved are patients, e.g. with anticancer therapeutics. The phase I trials are designed to determine the metabolic and pharmacologic profiles of the agent in humans, to identify possible side effects, and, if possible, to gain evidence of drug effectiveness. Phase I studies are typically single blind-studies, and they are intended to minimize potential risk to future exposition, providing sufficient information to enable the design of scientifically valid phase II studies (25).

b. **phase II (therapeutic exploratory) -** controlled clinical studies are performed to evaluate the effectiveness of the drug in a specific disease, and to define an effectiveness dose that provides the optimal benefit-risk profile. These studies typically involve several hundred patients (25).

c. **phase III (therapeutic confirmatory) -** are performed large-scale clinical studies, involving several thousand patients. The main purpose of these studies is to confirm the effectiveness and safety findings from previous studies (25).

d. **phase IV (therapeutic use) –** the aim of these trials is to provide additional information regarding the product's safety, efficacy, or manufacturing processes. They are conducted after marketing approval (25).

After the completion of clinical trials process – until phase III, all data obtained from manufacturing, preclinical and clinical studies are summarized, and the sponsor submits the request for marketing authorisation (25).

The process of drug development is expensive and time-consuming. An alternative development paradigm referred to as "quick win, fast fail" paradigm of drug development is proposed as a specific strategic to improve industry R&D productivity (15). In this new paradigm, the technical uncertainty is intentionally decreased before the expensive later

development stages (Phase II and Phase III) through the establishment of proof-of-concept (POC) (15). POC clinical trials are carefully designed to establish the safety of drug candidates in the target population and explore the relationship between the dose and desired activity, as either measured directly or by means of a surrogate endpoint (26).

In "quick win, fast fail" paradigm of drug development (figure 3), a reduced number of new molecular entities entering Phase II and Phase III advance with a higher probability of technical success. Any savings gained from this paradigm can be reinvested to further enhance R&D productivity (15).

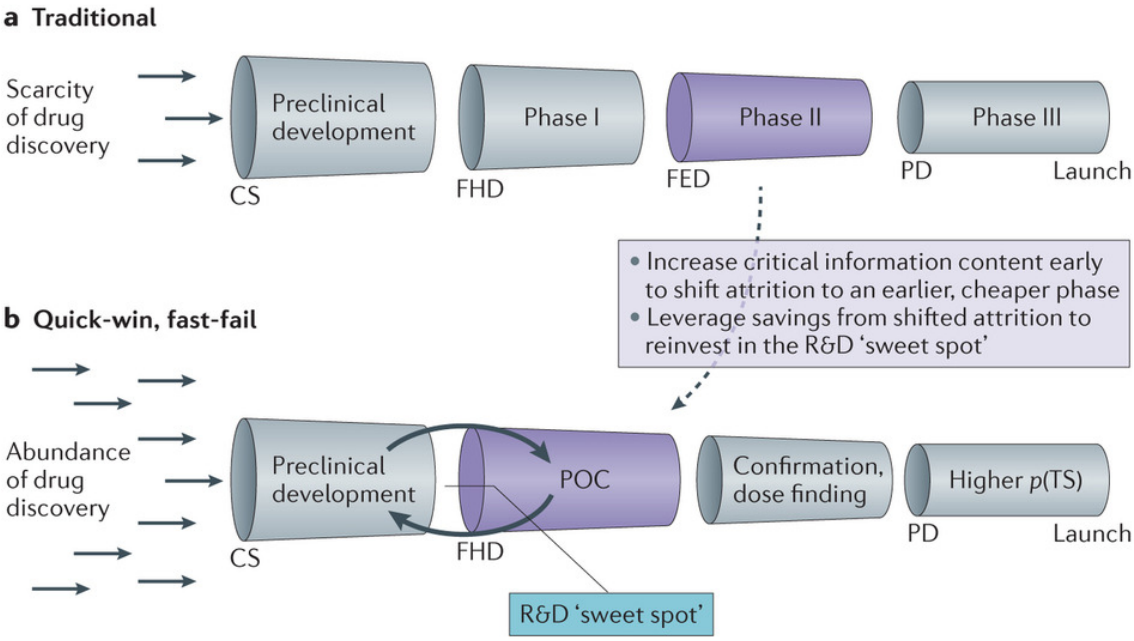

Figure 3 The traditional drug development model **(part a)** and an alternative, the quick-win, fast-fail model **(part b)**.

CS candidate selection; **FED** first efficacy dose; **FHD** first human dose; **PD** product decision;

Adapated from (15).

4.4. CLINICAL TRIALS IN PORTUGAL

Clinical trials are considered a keystone for economy, providing early access to innovative medicines to patients (27).

In Portugal, between 2006 and 2012, the number of submission of clinical trials to Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED) decreased 26%, from 160 to 118 studies. In 2011, while Europe experienced a small average market growth of 2.6%, only 88 studies were submitted. However, during 2012, there was a slight and progressive recovery (27). Regarding of submission request to clinical trials in Portugal, between 2013-2014, there was a growth of +11.1% and between 2014-2015, a growth of 10.8%. The number of authorized of clinical trials have also been growing, with 123 clinical trials authorized in 2015, when compared with only 99 in 2012. This increase occurs along with a decrease in the time of decision by competent authorities (28) (figure 4).

The analysis by phases of development shows that the majority of clinical trials performed in 2015 are Phase III studies and antineoplastic drugs and immunomodulators continued to be the therapeutic classes more studied (figures 5 and 6). This scenario not changed significantly since 2005. Moreover, it is interesting to highlight that, between 2012-2015, there was an outstanding increase from 3 to 15 Phase I studies, respectively (figure 5). However, the rate of clinical trials/million habitants in Portugal stills among the lowest of the Western Europe (28).

In 2013, PwC published a report about clinical trials in Portugal, which describes specific challenges of clinical trials conduction. The above-mentioned increase in Phase I-IV clinical trials has a relevant impact on Portuguese economy. For the clinical trials area, this gain is €1.98, which means that every €1 investment generated in clinical trials activity provides a return of €1.98 for the general Portuguese economy. This study estimates that the activity of clinical trials in Portugal had the potential to improve to as high as €143 million in 2015, if a series of current obstacles were overcome (27).

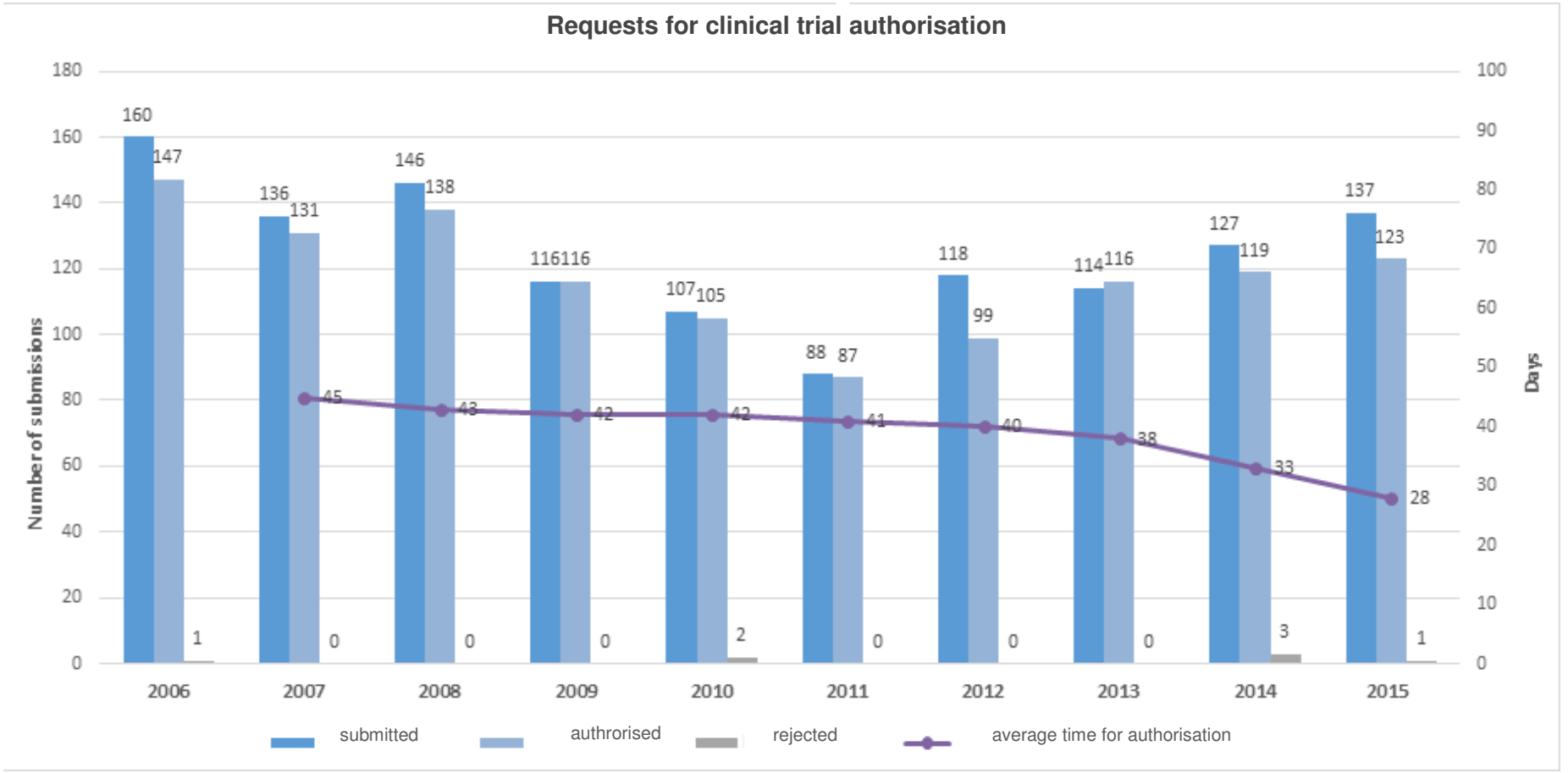

Figure 4 The number of requests for clinical trial authorisation

Adapated from Statistics of Clinical Trials between 2006 – 2015 http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS

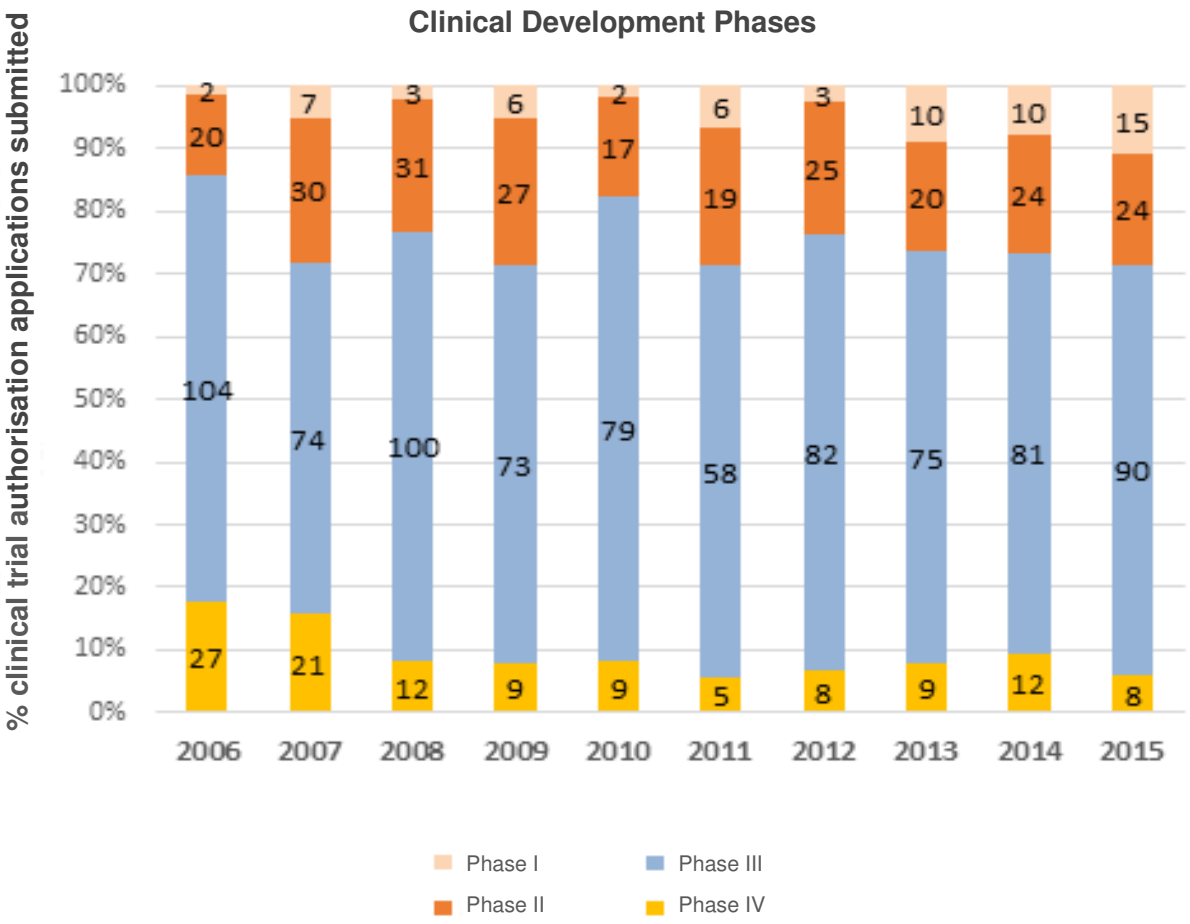

Figure 5 % clinical trial authorisation applications submitted to INFARMED, divided by clinical development phases

Adapated from Statistics of Clinical Trials between 2006 – 2015
http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS

The development of clinical trials in Portugal faces several barriers such as: a) the lack of recognition of the strategic importance of the clinical investigation to improve of health care and to contribute to the national economy; b) limitations of organizational, infrastructural and regulatory aspects; c) negative connotation of clinical trials; d) the low performance in recruiting patients (enrolment) by the clinical investigators; e) little competitive approval deadlines (27).

In Portugal, the lack of information of the clinical trials to the patients is considered one cause for the poor recruitment rates (27). Portuguese legislation restricts other sources of recruitment, such as mass media strategies via newspaper or radio advertisement (29).

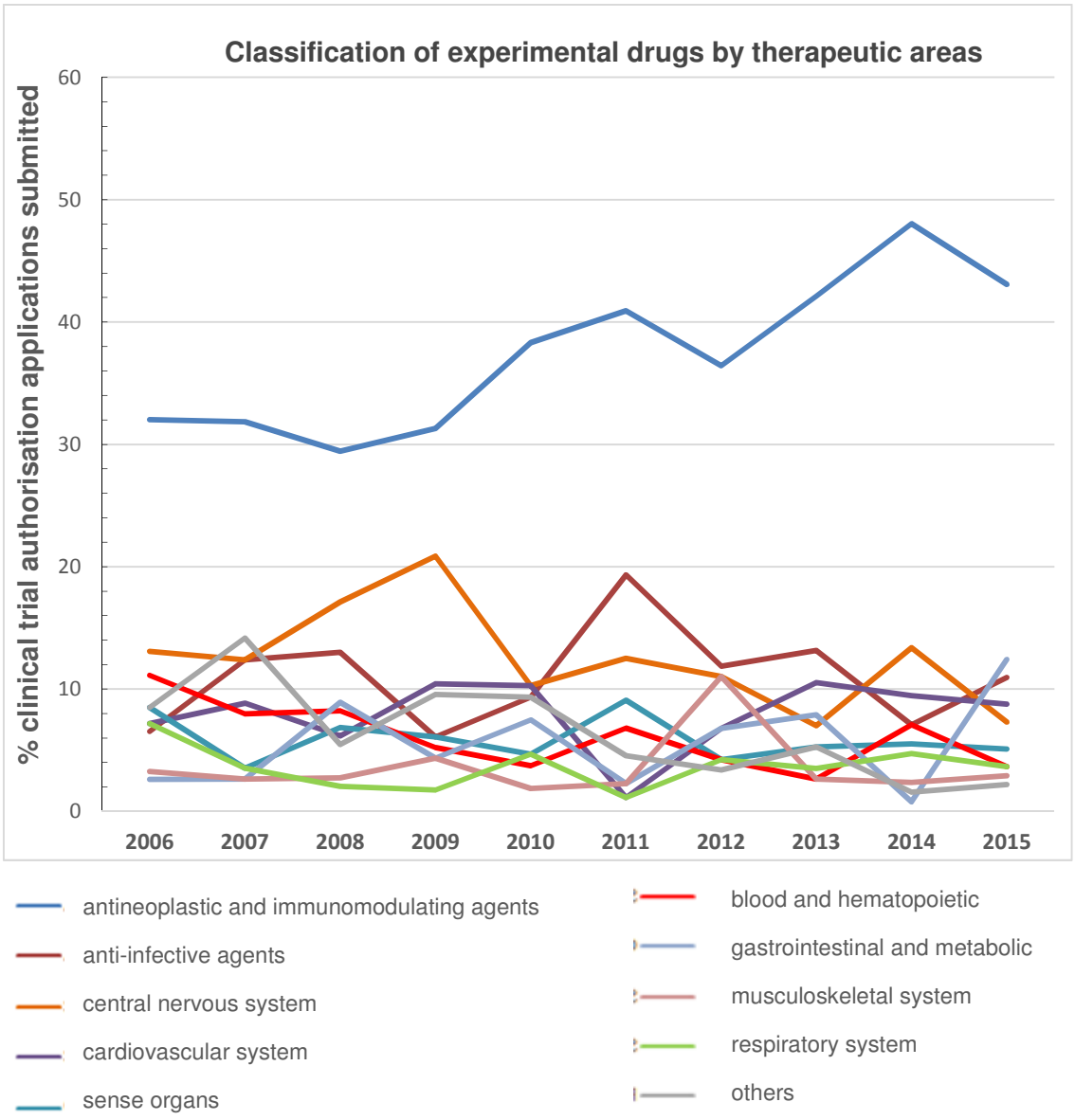

Figure 6 Classification of experimental drugs by therapeutic areas

Adapated from Statistics of Clinical Trials between 2006 – 2015
http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS

Then, the main source of recruitment is through the medical practice and medical references from professional colleagues (29). However, the “Plataforma Nacional de Ensaios Clínicos” was created to allow that the information about clinical trials stays more accessible (30).

The PwC report also proposes strategies to support the clinical trials in Portugal, such as the development of an independent organisation dedicated to clinical research, a national health education and clinical trials disclosure strategy, and the inclusion of clinical research in professional careers (27).

5. ON THE JOB TRAINING

5.1. GENERIC TRAINING

This sub-chapter outlines the generic training performed in different fields, which provided the basic knowledge and skills for study coordination activities. In the following sections, it will be mentioned the Good Clinical Practice (GCP) training, the Dangerous Goods training, and it will also be presented an overview of the clinical trials regulatory framework. Moreover, the training in electronic data capture and interactive response systems will be presented, as well, due their relevance to the conduction of the trial.

5.1.1. GOOD CLINICAL PRACTICE

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with the GCP provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. It also ensures that the clinical trial data are credible (31). This course is performed online, and it is mandatory to integrate the research team, as study coordinator. The GCP training must be completed at a minimum of every 3 years.

5.1.2. DANGEROUS GOODS TRAINING

This training is mandatory for the preparation and shipment of dangerous goods, including for the shipping of category A substances, infectious substance affecting humans, category B substances and biological substances. The online course presents the regulations imposed on most laboratories and highlights their importance, classifies the infectious substance for transport, demonstrates the procedures for legally and safely shipping of various infectious specimens and integrates dangerous goods procedures into laboratory. At the end, there is a self-assessment quiz to obtain the certification. This certification is valid for two years (32).

5.1.3. CLINICAL TRIALS REGULATORY FRAMEWORK

The clinical investigation is a highly regulated area, as set out in several guidelines, regulations and directives, as mentioned below.

The Declaration of Helsinki, a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data, was developed by The World Medical Association (33). The first version was adopted on June 1964, and then, several revisions and two clarifications were made.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a project involving regulatory authorities of Europe, Japan and USA and experts from the pharmaceutical industry. The guidelines from ICH are divided into four topics in order to facilitate the search of a specific guidance: Safety, Quality, Efficacy and Multidisciplinary. The main purpose is to achieve global harmonization, but these guidelines are not mandatory (34). The ICH GCP guideline E6(R1) was published in 1996, and describes the responsibilities and expectation from the main involved parties (investigators, Clinical Research Associates (CRAs), sponsors and Ethics Committees) in clinical trial conduction. It is an international standard to ensure the compliance with GCP for designing, conducting, recording and reporting trials involving humans (35). Current, it was voted the adoption of an addendum to guideline for ICH GCP E6(R1). This addendum (E6(R2)) aims to encourage sponsors to implement improved oversight and management of clinical trials, while continuing to ensure protection of human subjects participating in trials.

In the EU, all clinical trials performed need to be conducted in accordance with the Clinical trials Directive 2001/20/CE, until the implementation of the new Clinical Trials Regulation EU no.536/2014, that was adopted on 16 June 2014 (it is expected to be in force by October 2018). The Directive 2001/20/CE was elaborated in order to approximate laws, regulations and administrative provisions of all Member States (MSs), related to the implementation of good clinical practice in the conduction of clinical trials on medical products for human use (36). However, it has often been criticized as having excessive bureaucracy, and it did not achieve its goals because it was implemented differently in MSs. This Directive was transposed to Portuguese legislation to law no.46/2004 of 19th August, which was repealed by law no. 21/2014, of 16th April, and this last one was changed by law no.73/2015, of 27th July (37).

The new regulation no.536/2014 will ensure that the rules for conducting clinical trials are identical throughout the EU, namely the assessment of applications for clinical trials, which is divided in two parts. Part I is jointly assessed by all MSs concerned. Part II is assessed by each MS concerned separately. Besides this, the purpose of the regulation is improving timelines and flexibility, increasing transparency and supporting more information to the citizens of Europe. Overall, this regulation intends to eliminate the current obstacles in the current directive (38).

The EU Clinical Trials Regulation has also taken up certain requirements from two others relevant Directives:

- Commission Directive 2005/28/EC, of 8th April 2005 – sets out 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;

- Commission Directive 2003/94/EC, of 8th October 2003 – defines the principles and guidelines of Good Manufacturing Practice in respect of medicinal products and investigational for human use (38).

Portuguese law no.102/2007, of 2nd April is a transposition into internal legal order of Directive no.2005/28/EC. Besides the above-mentioned national legislation, it is also relevant to consider the national law no.67/98 of 26th October about personal data protection, a transposition of Directive no.95/46/CE of 24th October 1995 (39).

5.1.4. ELECTRONIC DATA CAPTURE SYSTEMS

In clinical trials, there are different systems adopted by pharmaceutical companies and Clinical Research Organization (CRO) to collect clinical data in electronic format – the electronic Case Report Form (eCRF). The different systems, such as Medidata Rave®, Inform™, Oracle® and DataTrack™, require online training and an assessment quiz. These trainings gave me the skills to use them in an efficient way, namely reporting the patient's data with accuracy.

5.1.5. INTERACTIVE RESPONSE SYSTEMS

Interactive Voice/Web Response System (IVRS/IWRS) helps in handling the logistical issues related to the conduction of clinical trials. IVRS implies the use of telephone, and provides automated confirmation of assignments by fax. On the other hand, the transaction in the IWRS is performed in an online system, and the confirmation report is sent by e-email or fax.

The web-based system is the most used, due the accessible anytime through an internet connection. This system allows the drug supply management, the patient enrolment and randomization and the dispensation of the study drug. When applicable, it is also performed in the system the registration of an unscheduled visit, the discontinuation of the treatment or an unblinding procedure. Screening failures are also registered in the IWRS/IWRS system. There are different examples of IVR/IWR systems, such as ClinPhone®, Almac® and EndpointClinical®.

5.2. SPECIFIC TRAINING

The aim of this sub-chapter is to describe the activities performed in the scope of clinical trial coordination, integrated in a broader description of the related processes of a clinical study. Additionally, it will also be summarised in which clinical trials and observational studies I was involved, and what type of tasks and activities were performed in each study. The activities that I performed during the training are described in table 1.

The clinical trial coordination activities will be presented through the perspective of a clinical research centre, according to the stage of implementation and conduction of a clinical study. This process can be divided into: initiation, conduction and close out activities.

5.2.1. CLINICAL TRIAL INITIATION ACTIVITIES

The initiation process of a clinical trial at site includes a wide range of activities and processes namely: a) the signature of a confidential agreement; b) the completion of the feasibility questionnaire; c) the qualification visit; d) the preparation of submission

Table 1 The activities performed as CRC during the training.

	Study visits					Other activities				
	ICF	**Screening**	**Randomisation**	**Treatment**	**End of Treatment**	**Submission phase**	**eCRF**	**Monitoring visit**	**Documents management**	**Sample shipment**
ONCOLOGY										
SELECT-1				x	x		x	x	x	x
INCYTE				x	x		x	x	x	x
FLAURA	x	x	x	x	x		x	x	x	x
MO29750	x	x	x	x			x	x	x	x
MK3475-091						x		x	x	
BI 1302.5						x		x	x	
M12-914	x	x	x	x			x	x	x	x
HEMATOLOGY										
CHRONOS-3	x	x						x	x	
B3281006	x	x						x	x	x
IMAN								x	x	
GASTROENTEROLOGY										
MLN0002-3026						x			x	
CT-P13						x			x	
NEPHROLOGY										
Dolomites	x	x	x	x			x	x	x	x
OPHTHALMOLOGY										
SALT	x	x	x	x			x	x	x	x
INTERNAL MEDICINE										
NAVIGATE	x	x	x	x			x	x	x	
Carmelina				x					x	x
GPD0101	x	x					x			x
DERMATHOLOGY										
Optimise	x	x	x	x		x	x	x	x	x
PNEUMOLOGY										
Dynagito				x	x				x	x
Estair	x	x		x			x		x	x
Arietta						x			x	
REUMATOLOGY										
CT-P10 3.2	x			x	x					
DS5565-A-E310	x	x	x	x	x					

documents and the analysis of the financial contracts; e) the clinical trial approval; f) the investigator meeting; f) the clinical trial initiation visit.

FEASIBILITY QUESTIONNAIRE

First of all, after a new proposal to a new study is received, it is necessary to identify who is/are the physician(s) from the site that can have interest in the study. This new proposal can be received from three different sources, such as: a) directly by the sponsor; b) through the CRO to which the sponsor delegates the responsibility for selecting the suitable sites; c) from the Blueclinical's back-office. In some cases, the sponsor or the CRO contacts directly the physician. The above-mentioned proposal is sent with a brief summary of the study and with the confidentiality agreement. This agreement is signed by the Principal Investigator (PI), in order to ensure the confidentiality of the process. Only after this, it is sent more information regarding the study, namely the protocol synopsis and the feasibility questionnaire to the interested physician. This feasibility questionnaire is an assessment tool to determine the site's conditions to perform the study. Moreover, it is also required information concerning the standard of care, the patients' recruitment potential, the infrastructures and the facilities of the site, and also the human and material resources available. After the feasibility questionnaire has been answered, it is necessary wait until to receive information regarding the selection of the clinical research site (40).

QUALIFICATION VISIT

When the clinical research site is selected to be one of the possible sites to conduct the clinical study, the CRA or other element from the sponsor or CRO representative requires the schedule of a qualification visit. All departments involved in order to fulfil the protocol requirements should be present, e.g. the Pharmacy, the department of Clinical Pathology, the department of Anatomy Pathology and the department of Imagiology, if applicable. The qualification visit is performed to a) assess if the site's interest in the clinical trial remains; b) review the site adequacy to perform the study and the access to target population; c) inquire the training and experience of the study staff. Moreover, during this meeting, it is also presented the study objectives, the protocol-required procedures and is discussed with the investigators the inclusion and exclusion criteria (41). Regarding the observational studies, the qualification visit is usually performed by phone, between the CRA and the PI.

SUBMISSION PHASE

After the qualification visit, it is necessary to wait until receive the feedback about selection. If the site is selected to participate in the trial, the submission process is initiated with the preparation of the required documents. These documents are mandatory to obtain approval of a clinical trial from all competent authorities (CEIC, INFARMED and CNPD) in Portugal (figure 7). The negotiation of the financial contract for submission to the AB of the hospital is performed by Blueclinical's back-office.

During the submission phase to the competent authorities and to AB of CHVNG/E, the following documents are mandatory:

a. **authorisation submission letter** – is elaborated by the sponsor or sponsor´s representative, and asks permission to conduct the clinical trial at CHVNG/E. It is also presented a summary of the study.

b. **sponsor statement** – this letter presents the status of approval of the trial by the competent authorities INFARMED, CEIC and CNPD. Additionally, it is also included a statement that the sponsor will only initiate the trial when every authorisations are gathered.

c. **declaration of site conditions** – a statement that indicates that every departments of the hospital involved in the trial have the adequate conditions, namely the equipment, the facilities and the human resources required. This declaration is signed by the PI and by all the Head of departments involved.

d. **declaration of the recruitment's modality** – a document where the PI states how the patients that fulfil all the inclusion criteria will be identified, and that the recruitment will only be performed by the investigators.

e. **declaration of participant's compensation** – a statement signed by the PI referring that only the expenses incurred due study participation are reimbursed to the participants.

f. **investigational product circuit** –defines who is responsible for perform the different tasks (the supply, the reception, the storage, the prescription, the preparation, the dispensing, the administration, the devolution and the destruction) related with the IMP. This document is discussed between the CRA and the Pharmacy.

g. **declaration of conditions from the Pharmacy** –the Head of the department states that the pharmaceutical department has the adequate conditions to perform all the activities related with the IMP.

h. **PI Curriculum Vitae (CV)** – A PI CV referring the PI's experience in clinical trials, the professional experience, the GCP training and any other relevant information for the matter.

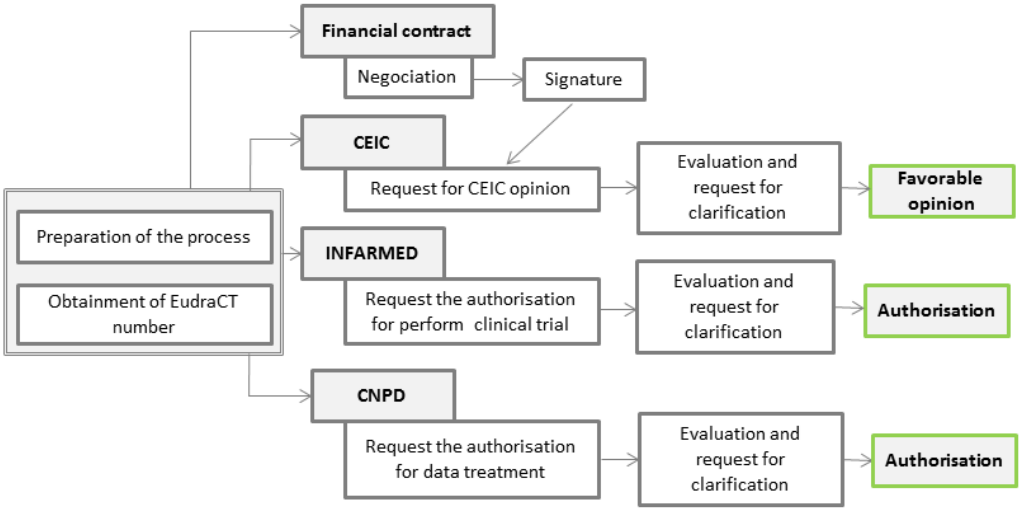

Figure 7 Approval process for clinical trials in Portugal.

Simultaneously, the financial contract is reviewed and negotiated by Blueclinical's back-office. This document defines the economic aspects, namely the direct and indirect costs of the study, the payment period and all conditions established between the parties. Moreover, it is also stated in this document, the confidential and publication policies. The research team members, the payment percentages, the recruitment goal and other relevant information are addressed to the back-office by the CRC.

The submission process for observation studies has some differences. The observational studies are evaluated by the AB and by Ethics Committee at CHVNG/E – Comissão de Ética para a Saúde (CES), and by the CNPD. In this case, any document related to pharmacy and IMP is not applicable.

INVESTIGATOR MEETING

For most of the clinical trials and observational studies, an Investigator Meeting (IM) is organized by the clinical trial sponsor. All the investigators and site personnel from each site participating in the clinical study should be present. In this meeting is addressed information regarding the pharmacology of the IMP and also updated the clinical information of compound. Moreover, it is presented the study protocol, is explained the study design and other clinical trial procedures, and is provided training in therapeutic area, eCRF and other tools like the patient-reported outcomes (PROs) (42). These meetings are also an opportunity to contact with others clinical research team members, and to learn with their knowledge and experience.

During my internship, I had the opportunity to attend in two IM, both for clinical trials in patients with lung cancer (the first one was performed in Barcelona, Spain and the second was performed in Frankfurt, Germany).

SITE INITIATION VISIT

The site initiation visit (SIV) is required to prepare and set up a research site to conduct the study. This visit occurs usually after all required approval from the competent authorities and the AB (figure 7). This meeting is scheduled according the availability of the research team, including the representative's availability of each hospital department involved (41). Before the SIV, some pending issues for the trial initiation at site must be solved. Each member of the research team must complete all required trainings and must activate the accesses to the platforms – e.g. eCRF and IWRS. Moreover, CVs of research team and the signature of the financial disclosure must be obtained and filed. Some of these requirements are not applicable for observational studies.

CRA or another sponsor representative is responsible for conducting the SIV. During this meeting, the following topics are presented:

a. **the study protocol:** the objectives and the study design, the inclusion and exclusion criteria, the strategies and the targets of recruitment, the recruitment timelines and the study-specific procedures;

b. **the investigational product:** the dispensing, the preparation, the administration and the unblinded procedures, if applicable;

c. **the laboratory procedures:** the sample collection, the requirements for the processing and the shipping of biological samples to central laboratory, the supplies of central laboratory kits, the overview of the laboratory manual and the shipping materials;

d. **the safety reporting:** the procedures to report and to record serious adverse events (SAEs) and adverse events;

e. **data collection:** the eCRF and PRO, if applicable (41).

In this visit, all research team members sign the delegation log and the training log. The delegation log is a document where "the investigator should maintain a list of appropriately qualified and trained persons to whom the investigator has delegated significant trial – related duties" (43). The training log includes the people that have received training by attending to this meeting. If, for some reason, any element of the research team cannot be present at SIV, he/she will receive training by a member of the team who has been present in the initiation visit.

After the SIV, in most cases, the site is ready to initiate recruitment strategies and to begin enrolling patients. This confirmation is sent by e-mail from the sponsor. In some particularly cases, this not occur due some pending issues, e.g. legal approvals missing, web portal account activation missing.

5.2.2. CLINICAL TRIAL CONDUCTION ACTIVITIES

RECRUITMENT PERIOD

The expected number of patients to include in the study and the recruitment timeline is presented during the SIV. Once the recruitment period is opened, it is investigators' responsibility to recruit patients that meet all the inclusion criteria, and none of the exclusion criteria for the study. However, the CRC can contribute to the patient recruitment.

During my internship, I adopted two different strategies in order to identify potential patients, such as the analysis of clinical processes and the attendance in the consultation group. In the analysis of clinical processes, I read the clinical data of patients and checked the eligibility criteria of the study. After this review, the patient is flagged, and this information was addressed to the investigator. It is relevant highlight that, all the criteria

are then verified by the investigator. When a potential patient was identified during the consultation group, the eligibility criteria were analysed, according to the clinical data of the patient available. In these meetings, it also was emphasised the flowchart of the events and the essential aspects related to the treatment proposed to the investigator. This information was addressed to the patient during the medical consultation, where the informed consent form (ICF) was presented and the patient advised to take home the document, read it carefully and to identity doubts to be clarified.

SCREENING

The screening is a period of time (days or weeks) used to assess the patients' compliance with the protocol criteria. First of all, the physician must clarify all doubts of the patients regarding the ICF and/or the study. If the patient agrees to participate and to sign the ICF, this information needs to be registered in medical records. It must be registered how the ICF was presented, must be detailed that all the doubts were clarified and that two copies of this document are signed. One copy of the ICF is given to the patient, and another is kept in the Investigator Site File (ISF). If the patient was unable to sign the document, two independent witnesses or the legal representative can sign and can date the documents. Only after this, all screening procedures according to the protocol requirements can be performed and/or scheduled.

The inclusion of the patient in screening of the study need to be registered in the IWRS or IVRS, according to the protocol procedures, by the CRC. These systems attribute a screening number to the patient.

The next step is to schedule the exams, the laboratory analysis and other procedures required by protocol. It is crucial to ensure that the results of the exams and the laboratory results are available within timeline defined in the protocol to randomise the patient.

RANDOMIZATION

In another medical consultation, the investigator assesses the results of the exams and/or laboratory analysis, and checks the eligibility criteria worksheet with the inclusion and exclusion criteria. If the patient meets all inclusion criteria, and none of the exclusion criteria, the patient is randomised through the IVRS/IWRS. The randomisation is the allocation method of patient population into groups that will receive different interventions which may be test or control groups. The aim of this method is to avoid the bias, assuring

that subject populations are similar in all groups, to minimise systemic differences between groups that could affect the outcomes and to provide a powerful basis for statistical inference. If the patient does not meet the eligibility criteria, the subject is considered a screening failure, and this also need to be registered in the IVRS/IWRS (44).

PATIENT VISITS

Some activities related with the patients, namely scheduling, preparation and supporting the visits and/or other procedures are performed by the CRC. These visits and all the procedures required must be performed in accordance with the periodicity defined in the protocol.

The analysis of the study flowchart is essential to schedule the procedures and to prepare the clinical visits. Usually, it is necessary to contact the patient a) to communicate date and time of blood tests and other procedures, e. g. computerised tomography electrocardiogram or blood tests, b) to remember the patient to bring to the site the unused study medication and the medication diaries and c) to alert the patient to be fasted for biological collection, if applicable.

The preparation of the visits comprises the elaboration of a checklist in Microsoft Word document for each visit. This guide contains a list of all topics needed to record in clinical process of patient by the investigator, in order to fulfil the protocol. In this template, it is also provided the next date of patient visit and/or study procedures, e.g. blood samples collection, next treatment or computerised tomography. Additionally, sometimes it is also elaborated a guide with all procedures to be performed per protocol. With this methodology, the records are more accurate and complete. All members of the research team that will perform any procedure in the visit are informed with the adequate information by e-mail, phone or in person.

During the patient visit, it is necessary an exceptional articulation between all team members to perform the procedures required per protocol. Besides the medical consultation with the investigator, the protocol may require the collection of biological samples, the dispensation of medication and/or other procedures e.g. perform a 12-lead electrocardiogram or a spirometry. When it is required collection of blood, urine or others biological samples, the laboratory kit provided by the sponsor needs to be available and the tubes identified with the subject number. This laboratory kit is delivered previously to the study nurse. After the collection, the biological samples, if applicable, are processed in

local laboratory and then, they are sent to central laboratory. All procedures are performed according to the information available in Laboratory Manual of each study. In this manual, it is also specified if the biological sample is sent in ambient temperature or frozen. The frozen biological samples are sent in a package with dry ice, which needs to be requested previously. The packaging and the sending of the samples through the courier are responsibility of the CRC.

Regarding the drug dispensing, the IVRS/IWRS may be use to assign the medication. Two copies of the report of IVRS/IWRS drug dispensing are printed. In this report is presented the subject clinical trial identification, the treatment assigned and the batch number, if applicable. In addition to this report, the investigator also signs and dates the prescription form. Then, these two documents are delivered to the Pharmacy. If applicable, the return medication of the last period treatment is also delivered to allow the determination of compliance. The determination of treatment compliance is relevant to the results of the study.

DATA ENTRY

After each patient visit, source data is introduced in Case Report Forms (CRFs), which may be in paper or electronic. However, during my internship, I always worked with eCRFs. Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial, and is necessary for the reconstruction and evaluation of the trial (45). This data should be: a) accurate, b) legible, c) contemporaneous, d) original, e) attributable, f) complete, g) consistent, h) enduring, and i) available when needed. Thus, the elaboration of a template guide to the patient visits helps to achieve some of these attributes (45). After patient visit, source date is organized in the patient file, and then introduced in each CRF page.

During my internship, I performed data entry of many clinical trials and observational studies. Sometimes, some information was missing or was not totally clarified in patient's records. In these cases, I took note, and then inquired the investigator to complete the patient's records.

When data entered does not pass in validation rules, the eCRF or the sponsor reviewers generate a query. A query requests to the investigator and/or CRC to review and/or to clarify the information introduced. The respond to queries must be done urgently in order

to ensure that results can be reported. First I always checked and reviewed the source data, and thereafter I modified data entered or clarified the information introduced.

SAEs REPORTING

SAE is any untoward medical occurrence that at any dose:

- results in death, or
- is life-threatening, or
- requires inpatient hospitalization or prolongation of existing hospitalization, or
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly /birth defect
- is a medically important event.

In the case of occurrence of a SAE in the course of the study, then Investigator or other site personnel must inform the sponsor representative within one day, i.e. immediately but no later than 24 hours of when he or she becomes aware of it. The initial report is completed by investigator with the information available, ensuring that the patient's identity is protected. The following information is relevant for reporting a SAE: a) the date of onset and the end date, b) the causal relationship with the trial medication, c) the intensity (mild, moderate or severe) and d) the outcome of the event. Sometimes, the information available is incomplete within 24 hours. Thereafter, as soon as new information is available, a follow-up report needs to be sent. In the report should also be sent in attachment all examinations carried out, the laboratory results and the hospitalization reports, if applicable. All the information related with the SAE need also be entered within the same period of time in the appropriate forms of the eCRF (43) .

MONITORING VISITS

The main purpose of monitoring visits is to verify and to oversee the progress of the clinical trial and to ensure that it is being conducted, recorded and reported in accordance with the protocol, the GCP and the applicable regulatory requirements. More specific, the objectives are:

a. to ensure the protection and well-being of human subjects;

b. to guarantee that reported trial is accurate, complete and verifiable from source documents;

c. to verify the clinical trial compliance with protocol/amendments, GCP and regulatory requirements (41).

Therefore, before each monitoring visit, the patient file(s) is/are reviewed, the missing data is introduced and other outstanding issues, related e.g. with queries, are resolved. The patient file(s), the subjects' medical processes and the ISF need to be available during the monitoring visit. The investigator(s) and the CRC need also to have time to answer any doubts and to clarify any information. However, sometimes it is not possible to solve all the issues. After the visit, the monitor sends a follow-up letter, where it is described the unsolved issues. I always used this letter as guidance in order to solve the pending issues, as soon as possible.

During this visits, the monitor can also provide training to any new element of the research team and/or regarding a new protocol amendment. Moreover, the monitor can also highlight any problematic question of the protocol.

5.2.3. CLINICAL TRIAL CLOSE-OUT ACTIVITIES

CLOSE-OUT VISITS

The close-out visit is only performed after the last patient had completed the scheduled visits defined per protocol. First, the sponsor defines the different timelines to complete the CRF, to solve queries, and when the database will be locked. A notification of the end of the study is sent to the investigation team. The data introduced in eCRF is reviewed, and I need to be with attention to CRF to solve, as soon as possible, all queries (41). Sometimes, this task involves the revision of source documents from the beginning of the clinical trial/observational study. Then, in the close-out visit, all the documents, including the ISF and the patient file are verified and any outstanding issues are resolved. In the end of data revision, the PI can sign the CRF (41). The PI must also be available during the close-out visit to sign and date all documents. These documents must be archived in order to be accessible in the future upon request, during an audit or an inspection. The essential documents of the clinical trials should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or

contemplated marketing applications. However, the period can be longer according the agreement between the sponsor and the PI.

All equipment and materials assigned to the hospital during the trial are returned during this period. Unused biological sample kits are destroyed.

Regarding the observational studies, the close-out visit is very similar of a clinical trial.

6. DISCUSSION

In this chapter, I will present my reflections regarding the internship and I will discuss if the learning goals have been achieved. In addition, I will also present the difficulties that I experienced and I will identify the strategies adopted to solve the problems.

The internship was an opportunity to transpose the scientific and the theoretical knowledge acquired during the Master to the practice of the clinical research. This was a challenging and an exciting experience because represented a new period in my professional life. Moreover, during the internship I assumed the responsibility of being primary CRC in some therapeutic areas (oncology, hematology, nephrology, gastroenterology and vascular surgery). This contributed to the increase of my responsibilities at site, but also to have conscience of the importance of my work to improve the clinical research at CHVNG/E. Besides these therapeutic areas, I had the opportunity to conducting activities in other therapeutic areas. I also gathered experience in conduction clinical research activities in rheumatology, dermatology, internal medicine, pneumology and ophthalmology trials.

I recognize that a previous knowledge about the clinical trials process accelerated my gain of autonomy to perform the CRC activities. However, at the beginning of the internship, I took time to learn the working procedures, the structure and the organization of the clinical research site. This information was essential in order to define the goals of my work, to prioritize my tasks and to adapt and to flexible my work methodology. Additionally, I understood that a progressive knowledge about the pathological aspects and the treatment guidelines of several diseases helped me in my activities/tasks. This knowledge helped me during my pre-screening activities, e.g. the analysis of the clinical patient files and attendance in the consultation group, and facilitated the communication with the investigators regarding the potential subjects to enrol in a clinical trial.

At the beginning of my internship, I also needed the guide and the help of my colleagues to integrate me in the research teams and to perform the activities/tasks. I realized that the team work has a critical role to perform the clinical coordinator activities and to promote clinical research at site. The fact that the research team is constituted by several professionals with different ways of working and organisation is another relevant aspect to consider. Besides this, they need to conciliate the clinical investigation with the clinical practice. Therefore, I needed to adapt me to their schedules, to understand their work

methodologies and met their expectations. A good relationship and an excellent communication flow with all team members were critical to facilitate my work. Many times, it was necessary the help of other elements of the research team to manage several subject visits occurring simultaneously in different departments. In order to manage these situations, previously I analysed the protocol and articulated with these elements how the patient visit would be managed and which procedures would be performed. I also ensured that all worksheets and guidelines developed were available in time. These documents supported the subject visits and contributed to the quality of data.

I was always available to support any team member of the clinical research during his/her tasks. Moreover, I was always available to solve quickly any doubt or any pending issue, since I was the contact point between the research team, the monitor and all hospital departments involved in clinical research. During my internship, the progressive knowledge about the specific procedures of each clinical trial contributed to my ability to solve any new problem/doubt. For this, it was also very useful to understand the structure and the organization of the clinical research site, but also the identification of the role of each person in several departments.

The clinical coordination activities were organized and planned timely, considering the priority of each task. All clinical visits were carefully scheduled and prepared, ensuring that all timelines and procedures were compliant with the protocol. Besides this, I also understand that it is relevance the conduction activities according to the ICH guidelines and other regulations. The patient data recorded during the clinical visit was maintained updated in the source documents. They are appropriately archived and organized in the patient file, which facilitated the introduction of the data into CRF and helped to support the monitoring visits.

I established a personal contact and a good relationship with the patients. I realized the importance of demystification of the participation in a clinical study and the relevance of keeping a good flow of communication with them. During the screening visit, in some cases, I supported the investigator explication regarding the ICF and the procedures that would be performed during the trial. I also had an active participation during the patient visits. I was responsible to manage the procedures required by the protocol, to return the medication to the Pharmacy, and also to deliver it to the patient. However, sometimes conflicts situations emerged because the visits were too long. In these situations, I tried to identify the reason why it was taking so long, and explain it to the patient.

Another critical point, it is the collaboration with other elements outside of the hospital, such as the CRAs. The cooperation and the exchange of experience with the CRAs contributed to the gain of knowledge and competences to perform the clinical trials activities.

Sometimes, I had some difficulties due to lack of experience to deal with the unexpected situations, namely failure of electronic systems, changes in deadlines, among others. However, during my internship I gained experience in management and resolution of these types of issues.

In respect to my professional learning outcomes, I did not provide an equal contribution to all clinical trials coordination activities. I have gained more experience in performing the initiation and conduction activities, over the research site submission process and the close-out visits. The above-mentioned difference in the activities performed is related the fact that the submission process is conducted majority of the time by my colleague. Nevertheless, several times, I sent by email the explication of how perform the research site submission process and accompanied several times this task.

Several times during the internship, I had the necessity of to perform a critical analysis of my work methodologies, and I identified several aspects to improve my work efficiency. The main goal of this analysis was to develop the proposed activities in an effectively and efficiently manner. To help this, I adopted several strategies, such as to register all important events (patient visits, SIVs, monitoring visits, close-out visits) in my planner, a "*to do list"* with the pending issues and a Microsoft Excel page with the protocol procedures that is necessary to schedule with the different vendors. Furthermore, in a progressive way, I oriented the other elements of the research team to perform their activities in an autonomy way.

Unfortunately, I did not cooperate in any audit or inspection. I consider that they are an opportunity of learning and improvement. I also would like to help the development a clinical trial from investigator initiative, since the beginning.

During the internship I had the opportunity of training and developing skills and competences as CRC, in professional settings. Overall, I consider that my training objectives were achieved with success. Regarding the impact on my personal growth, the internship allowed me to acquire and to develop my interpersonal relationships and my teamwork, my critic spirit and my organization skills.

7. CONCLUSION

The internship as CRC represented an enriching experience since it allowed me to transpose and to consolidate the knowledge acquired during the Master. Besides this, I developed skills and competences as CRC, I strengthened my professional skills and my interpersonal relationships in professional settings. Additionally, it gave me a clear perception of the critical role of the CRC as element of the research clinical team. The role of CRC has become increasingly demanding, with trials and the environment where they are conducted becoming more complex every year. This is even more relevant, considering that in Portugal, the main reasons of the low performance in clinical trials field are due organizational and logistic problems.

During the internship, I had the opportunity to contact and to perform several activities according to the stages of the implementation and conduction of a clinical study (initiation, conduction and close out) in several therapeutic areas. In a progressive way, I gained experience and expertise in order to perform the above-mentioned activities in an autonomous way. At the same time, I developed several strategies to improve my work efficiency.

The internship required a dynamic and enterprising attitude. Then, I felt that I adopted a more proactive and assertive attitude, in order to promote clinical research at CHVNG/E. Simultaneously, I improved my problems solving skills and learned that even in adverse situations, it is necessary to achieve a solution.

My work was always performed in compliance with the protocol, the GCP, the ICH guidelines, and other relevant regulations. Moreover, in all situations, it was always considered the best interest and the welfare of the patient, and the quality of the clinical trials results.

Thus, I consider that the learning objectives previously defined were achieved with success. In conclusion, the internship fulfilled its purpose because give me the opportunity to develop competences and skills as CRC.

8. REFERENCES

1. Blueclinical [25 March 2016]; Available from: https://www.blueclinical.com/.
2. Blueclinical Research & Development. [25 March 2016]; Available from: https://www.blueclinical.com/rd/.
3. Blueclinical Phase I. [25 March 2016]; Available from: https://www.blueclinical.com/phasel/.
4. Blueclinical Clinical Research Partnership. [25 March 2016]; Available from: https://www.blueclinical.com/crp/.
5. Gabinete de Comunicação e Imagem do CHVNG/E. Área de Influência. [30 March 2016]; Available from: www.chvng.pt/index.php/chvng/area-de-influencia.
6. Gabinete de Comunicação e Imagem do CHVNG/E. História. [30 March 2016]; Available from: http://www.chvng.pt/index.php/chvng/historia.
7. Gabinete de Comunicação e Imagem do CHVNG/E. Organograma. 30 March 2016.
8. Kubiak C, Andres-Trelles F, Kuchinke W, Huemer K-H, Thirstrup S, Whitfield K, et al. Common definition for categories of clinical research: a prerequisite for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN). Trials. [journal article]. 2009;10(1):1-7.
9. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 Official Journal of the European Union.
10. Röhrig B, du Prel J-B, Wachtlin D, Blettner M. Types of Study in Medical Research: Part 3 of a Series on Evaluation of Scientific Publications. Deutsches Arzteblatt International. 2009;106(15):262-8.
11. Public Health Social Work. Types of observational studies. [7 April 2016]; Available from: http://ssw.unc.edu/mch/node/216.
12. Suvarna V. Phase IV of Drug Development. Perspectives in Clinical Research. 2010 Apr-Jun;1(2):57-60.
13. United S. Pharmaceutical R&D: costs, risks, and rewards. Washington, D.C.: Office of Technology Assessment, Congress of the U.S. : For sale by the U.S. G.P.O., Supt. of Docs.; 1993.
14. Getz KA, Kaitin KI. Chapter 1 - Why Is the Pharmaceutical and Biotechnology Industry Struggling? A2 - Buckley, Peter SchülerBrendan. Re-Engineering Clinical Trials. Boston: Academic Press; 2015. p. 3-15.

15. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. [10.1038/nrd3078]. 2010;9(3):203-14.
16. Remnant J. Measuring the return from pharmaceutical innovation 2014 - Turning corner? : Deloitte Centre for Health Solutions; 2014.
17. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov. [Analysis]. 2015;14(7):475-86.
18. The Innovative Medicines Initiative (IMI) Strategic Research Agenda 2005.
19. Mahajan R, Gupta K. Food and drug administration's critical path initiative and innovations in drug development paradigm: Challenges, progress, and controversies. Journal of Pharmacy and Bioallied Sciences. 2010 Oct-Dec;2(4):307-13.
20. IMI2. The right prevention and treatment for the right patient at the right time - Strategic Research Agenda for Innovative Medicines Initiative 2. . 2014 [17 April 2016]; Available from: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf .
21. Improving America's Heath. A survey of the working relationship between the life sciences industry and FDA. PwC. 2010.
22. Goldman M. The Innovative Medicines Initiative: A European Response to the Innovation Challenge. Clinical Pharmacology & Therapeutics. 2012;91(3):418-25.
23. Steinmetz KL, Spack EG. The basics of preclinical drug development for neurodegenerative disease indications. BMC Neurology. [journal article]. 2009;9(1):1-13.
24. Field MJ, Boat TF. Development of New Therapeutic Drugs and Biologics for Rare Diseases. 2010.
25. Ciociola AA, Cohen LB, Kulkarni P, the FDARMCotACoG. How Drugs are Developed and Approved by the FDA: Current Process and Future Directions. Am J Gastroenterol. [The Red Section]. 2014;109(5):620-3.
26. Al-Shurbaji A. Proof-of-Principle/Proof-of-Concept Trials in Drug Development. Pharmaceutical Sciences Encyclopedia: John Wiley & Sons, Inc.; 2010.
27. PwC. Ensaios clínicos em Portugal. 2013.
28. Estatísticas de Avaliação de Ensaios Clínicos pelo Infarmed. [23 April 2016]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS.

29. Ejiogu N, Norbeck JH, Mason MA, Cromwell BC, Zonderman AB, Evans MK. Recruitment and Retention Strategies for Minority or Poor Clinical Research Participants: Lessons From the Healthy Aging in Neighborhoods of Diversity Across the Life Span Study. The Gerontologist. 2011;51(Suppl 1):S33-S45.
30. Lei nº21/2014 de 16 de Abril - Aprova a lei da investigação clínica.
31. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice. . International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2015.
32. Dangerous Goods Training. Mayo Clinic - Mayo Medical Laboratories; [25 April 2016]; Available from: http://www.mayomedicallaboratories.com/education/online/dangerousgoods/.
33. World Medical A. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.
34. Edwards LD, Fletcher AJ, Fox AW, Stonier PD. Principles and Practice of Pharmaceutical Medicine: John Wiley & Sons; 2007.
35. EMA. ICH Topic E6 (R1) - Guideline for Good Clinical Practice. . 2002.
36. Europeia CdU. Diretiva 2001/20/CE Jornal Oficial das Comunidades Europeias[Internet] 1o maio. 2001:121-34.
37. INFARMED. Ensaios Clínicos. [23 April 2016]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS.
38. European Commission. Clinical trials - Regulation EU No. 536/2014. [26 April 2016]; Available from: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm.
39. Comissão Nacional de Proteção de Dados - Legislação Nacional. [23 April 2016]; Available from: https://www.cnpd.pt/bin/legis/leis_nacional.htm.
40. Rajadhyaksha V. Conducting Feasibilities in Clinical Trials: An Investment to Ensure a Good Study. Perspectives in Clinical Research. 2010 Jul-Sep;1(3):106-9.
41. Site Monitor Visits - Pre-Study Visits, Iniatiation Visits, Periodic Monitoring and Close-out Visits. [23 April 2016]; Available from: https://ccts.osu.edu/education-and-training-programs/research-education-and-training-programs/clinical-research-coordinator-resources/site-monitor-visits.
42. Research TIoC. Investigator Meetings. Hints & Tips for Clinical Research 4:1-2.
43. International Conference on Harmonisation Working Group, editor. ICH harmonised tripartite guideline: guideline for good clinical practice E6 (R1). International

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1996: Washington, DC.
44. Suresh KP. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. Journal of Human Reproductive Sciences. 2011 Jan-Apr;4(1):8-11.
45. Group GIW. Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials: EMA/INS/GCP/454280/2010. 09 June2010.