Universidade de Aveiro
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Secção Autónoma de Ciências da Saúde

DANIELA PATRÍCIA SIMÕES CABELEIRA

ESTÁGIO COMO COORDENADORA DE INVESTIGAÇÃO CLÍNICA NA BLUECLINICAL, LDA

INTERNSHIP AS CLINICAL RESEARCH COORDINATOR AT BLUECLINICAL, LTD

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Professora Doutora Alexandra Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro e da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical Lda.

Dedico este trabalho aos meus pais, por terem sempre apoiado a minha formação académica, por me terem encorajado nos momentos mais difíceis, por terem tornado tudo isto possível.

o júri

Presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático da Universidade de Aveiro
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agradecimentos

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palavras-chave

Investigação clínica, ensaios clínicos, coordenador de investigação clínica, Blueclinical, *Clinical Research Partnership*

resumo

Este relatório descreve as atividades que desenvolvi no âmbito do meu estágio curricular na Blueclinical, Lda., na área de negócio "*Clinical Research Partnership*". O estágio teve a duração de 10 meses, durante o qual desempenhei funções de coordenação de investigação clínica em dois hospitais diferentes: no Centro Hospitalar de Vila Nova de Gaia / Espinho entre Julho de 2013 e Fevereiro de 2014, e no Hospital Garcia de Orta a partir de Março de 2014.

Este estágio insere-se no âmbito do Mestrado em Biomedicina Farmacêutica, da Universidade de Aveiro, e constitui o meu primeiro contacto com o mundo profissional.

Neste relatório é revisto o estado da arte da investigação clínica em Portugal e no Mundo. Posteriormente encontram-se descritas as principais atividades desempenhadas no estágio, que se relacionam com a coordenação de ensaios clínicos e alguns estudos observacionais, e também com a gestão e implementação de gabinetes de investigação clínica nos hospitais.

Este estágio foi uma ótima oportunidade a nível profissional, uma vez me permitiu terminar a minha formação académica já com uma experiência prática sólida.

keywords

Clinical research, clinical trials, clinical research coordinator, Blueclinical, Clinical Research Partnership

abstract

This report describes the activities developed during my internship at Blueclinical, Ltd, in the business unit “Clinical Research Partnership”. The internship lasted for 10 months, in which I performed clinical research coordination activities at two different hospitals: at “*Centro Hospitalar de Vila Nova de Gaia / Espinho*” between July 2013 and February 2014, and at “*Hospital Garcia de Orta*” since March 2014.

This internship is within the scope of the Master’s degree in Pharmaceutical Medicine, in the University of Aveiro, and it is my first contact with the professional world.

This report reviews the current state-of-the-art of clinical research, both in Portugal and Worldwide. Afterwards, there are described the main activities performed in this internship, which are related to the coordination of clinical trials and some observational studies, and also with the management and implementation of clinical research offices in the hospitals.

The internship was a great professional opportunity, as it allowed me to finish my academic background already with a solid practical experience.

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LIST OF ABBREVIATIONS

AB – Administration Board

AE – Adverse Event

CAPA – Corrective Actions / Preventive Actions

CDA – Confidentiality Disclosure Agreement

CEIC – "*Comissão de Ética para a Investigação Clínica*"

CHKS – Caspe Healthcare Knowledge Systems

CHVNG/E –"*Centro Hospitalar de Vila Nova de Gaia / Espinho*"

CIC –"*Centro de Investigação Clínica*"

CLIC – Clinical Investigator Certification

CNPD – "*Comissão Nacional de Proteção de Dados*"

CRA – Clinical Research Associate

CRC – Clinical Research Coordinator

CRF – Case Report Form

CRO – Contract Research Organisation

CRP – Clinical Research Partnership

CTCAE – Common Terminology Criteria for Adverse Events

CV – *Curriculum Vitae*

ECG - Electrocardiogram

EMA – European Medicines Agency

EU – European Union

GAGIC – "*Gabinete de Apoio ao Gabinete de Investigação Clínica*"

GIC –"*Gabinete de Investigação Clínica*"

HGO –"*Hospital Garcia de Orta, E.P.E.*"

IB – Investigator Brochure

ICF – Informed Consent Form

ICH – International Conference of Harmonization

ICH-GCP – International Conference of Harmonization – Good Clinical Practices

IMP – Investigational Medicinal Product

INFARMED – "*Autoridade Nacional do Medicamento e Produtos de Saúde, IP*"

ISF – Investigator Site File

IVRS – Interactive Voice Response System

IWRS – Interactive Web Response System

PD – Pharmacodynamics

PI – Principal Investigator

PK – Pharmacokinetics

R&D – Research and Development

SAE – Severe Adverse Event

SDV – Source Data Verification

SIV – Site Initiation Visit

SOP – Standard Operating Procedure

SQIC – "*Sistema de Qualidade em Investigação Clínica*"

SSV – Site Selection Visit

1. INTRODUCTION

This report covers my curricular internship in Blueclinical, Ltd, which is integrated within the scope of the Master's Degree in Pharmaceutical Medicine, at the University of Aveiro. The company is composed by three main business areas. One of them is Blueclinical CRP, standing for "Clinical Research Partnership". CRP is based in the creation of partnerships with Portuguese health institutions, promoting their growth, efficiency and excellence in clinical research with drugs and medical devices"(1). I developed the internship in this business area, working as a Clinical Research Coordinator (CRC) for 10 months. From July 2013 to February 2014 I worked in "*Centro Hospitalar de Vila Nova de Gaia / Espinho*", and since March 2014 in "*Hospital Garcia de Orta*", in Almada.

1.1. CURRICULAR INTERNSHIP OBJECTIVES

Before the internship I had only a conceptual idea about what it was to be a clinical research coordinator and about the scope of activity of Blueclinical. Posting that, the main objective I defined for the internship was to learn about the role of a CRC and understand clinical research coordination. As secondary objectives, I aimed to develop my communication skills as well as my sense of responsibility, time management, autonomy and problem-solving ability.

Only after a few time acquainting with the company and job role I have been provided with, by the company, I could define a new set of more specific goals:

- To understand all the phases of a clinical trial from the site's point of view, since the moment the site is contacted for feasibility, throughout the trial conduction itself, until close-out visit and archiving;
- To comprehend the practical application of the International Conference of Harmonisation Good Clinical Practices (ICH-GCP) and regulatory requirements;
- To establish a contact network with the hospital staff and Clinical Research Associates (CRAs) to promote easier communication;
- To have a good professional relationship will all co-workers both from Blueclinical and the hospital.

1.2. HOST INSTITUTION AND PARTNER HOSPITALS

1.2.1. BLUECLINICAL, LTD.

"*Blueclinical – Investigação e desenvolvimento em saúde, Lda*", throughout this report referred to as Blueclinical, is a Portuguese company headquartered in the city of Porto. It is composed by three core business units, covering different sequential phases of clinical research and all the value chain in clinical development: the R&D (Research and Development) unit provides consultancy to help basic researchers translating their discoveries into applied research, supporting the initial development; the Phase I unit supports the earlier development in human volunteers; the CRP (Clinical Research Partnership) supports research in confirmatory phases in Portuguese institutions. Thus, Blueclinical covers all processes, "from bench to bedside", turning out possible to get discoveries made in laboratory available to patients in real-life conditions. Besides these main areas, the company gets support from other departments, namely quality assurance, business development, medical writing and data management and statistics (1).

The company was founded only two-years ago, and it has two partners: "*Bluepharma, SA*" and Professor Luís Almeida. From Bluepharma, the company inherited the "blue", both the prefix and the colour of the company's logo. Below there is a description of each business area, with further detail in CRP as it was the unit of my internship.

BLUECLINICAL R&D

The R&D unit serves the purpose of translation between basic and applied research. There were many companies investing in "bench" research lately, mostly small sized, and whose results have translation potential. This means that new drugs are being discovered that lack the know-how for developing their molecules into drug products(2). Blueclinical R&D provides consultancy to these companies, some of them start-ups, in the development of their projects with the ultimate goal of commercialization(3).

Consultancy activities of Blueclinical R&D comprise the creation of pharmaceutical, pre-clinical, clinical, and regulatory development plans, preparation and follow-up of scientific advice, creation of the investigator brochure (IB) and experimental drug dossier, and helping the business development process and selection of portfolio(3).

Consultancy is provided for both medicinal products and medical devices.

BLUECLINICAL PHASE I

Blueclinical Phase I is a dedicated unit to phase I clinical trials, operating in a ward of Hospital da Prelada, Porto. The facilities are modern and renewed, providing all the necessary comfort and safety to conduct this type of research.

Blueclinical Phase I mission is to conduct phase I studies in healthy volunteers (at Hospital da Prelada) and early-proof-of-concept studies in selected patient populations (at other hospitals, specifically contracted as a clinical research site for such type of studies). Among those studies in healthy volunteers, the following are included: i) bioavailability/bioequivalence studies, to determine whether different formulations of the same drug are equivalent; ii) food-interaction studies, to determine whether a drug should be taken with or without food; iii) drug-drug interactions studies, to determine whether a drug affects or is affected by simultaneous use of other medication; iv) tolerability and pharmacokinetic studies, to know the potential adverse effects and how the human body handles and eliminates a drug.

To be able to perform these studies, the phase I unit is constantly requiring healthy volunteers. To apply to volunteer, a candidate must complete the form available in the website of Blueclinical, where all general information is also available (4).

As there are very few early-phase trials in Portugal, this unit can largely contribute to change this situation, thus bringing high-value to the country.

CLINICAL RESEARCH PARTNERSHIP

Previously named Blueclinical SMO (meaning Site Management Organization), this business area is the one where I developed my internship. It is based in the creation of partnerships with Portuguese institutions, with the aim of improving their activity in clinical research. Blueclinical CRP's mission is "to support the activity of clinical research partners, promoting their growth, efficiency and excellence in clinical research with drugs and medical devices"(1, p3). The CRP network counts with several entities, as shown in Figure 1. Blueclinical is not considered a Contract Research Organisation (CRO) as it is not a service provider. Instead, Blueclinical establishes win-win partnership relationships with affiliated Institutions with the main goal to accommodate all stakeholders' interests, namely: patients, investigators, institutions, sponsors, society and collaborators.

Figure 1 Entities associated to the CRP network

In each hospital of the network the partnership is concretized in an agreement of collaboration, leading to the creation of a structure dedicated to support clinical research activities, and whose name varies according to the institution's organogram. This structure aims to coordinate, support and develop clinical trials in the institution, strictly adhering to ICH-GCP, applicable laws and other ethical principles. In "*Centro Hospitalar de Vila Nova de Gaia / Espinho*" (CHVNG/E), the clinical research office was structured as represented in Figure 2, and similar structures are found in the remaining hospitals. The Clinical Research Office, (in Portuguese "*Gabinete de Investigação Clínica"* - GIC), is composed by a coordinator, a supporting office ("*Gabinete de Apoio ao Gabinete de Investigação Clínica*" - GAGIC), and all clinical investigators that desire to become associated with the office (5). The coordinator is a physician named by the hospital's Administration Board (AB), who will facilitate the integration of the office within the institution. GAGIC is formed by collaborators from Blueclinical CRP: a local Clinical Research Manager,

where applicable, and one or more CRCs that will perform the operational work of the office. Each Blueclinical collaborator must sign a confidentiality agreement with the institution, because there will be access to patient information, which is strictly confidential data. Associate Clinical Investigators are all physicians from the institution who wish to become associated with GIC and that undergo a training programme in clinical research, ICH-GCP and quality management. This training is named "Clinical Investigator Certification" (CLIC), and it is provided for free by Blueclinical. The office reports to the Clinical Operations Director of Blueclinical, which in turn reports to the management of the company. In "*Hospital Garcia de Orta*" (HGO), this office is named "*Centro de Investigação Clínica*" (CIC).

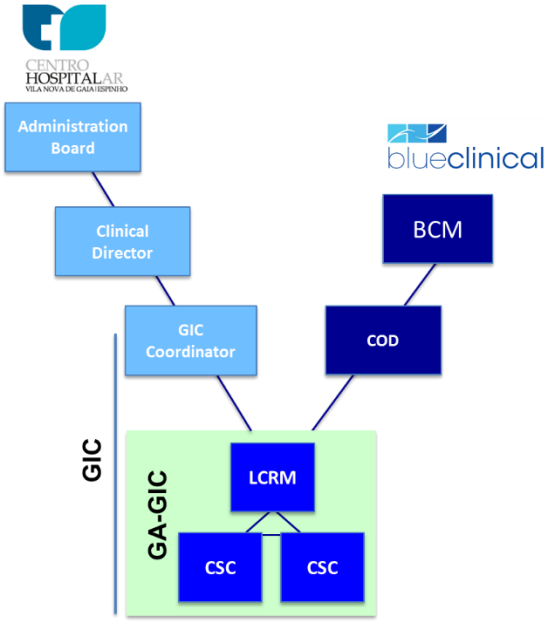

Figure 2 Structure of clinical research office of CHVNG/E.

The functions of supporting offices (e.g. GAGIC) are to deal with clinical trials submission processes, and then to support clinical teams in every administrative and logistical aspect related to the clinical trial (e.g. identifying patients, organising clinical visits, introducing data in CRFs (Case Report Forms), organising the Investigator Site Files (ISF), and also to keep tracking of the payments coming from research). They are also responsible for preparing eventual audits and inspections and implement Corrective Actions and Preventive Actions (CAPA) (5).These concepts will be discussed in the next sections.

Blueclinical CRP is also composed by a back-office that helps with the administrative duties of each office. Blueclinical supports clinical investigators in studies of their own initiative, by providing templates of essential documents, performing regulatory submissions, and then support the preparation of statistics and publication of results.

The two pillars of CRP are quality and training: one objective for Blueclinical CRP is to have a quality management system (SQIC – "*Sistema de Qualidade em Investigação Clínica*"), defining in Standard Operating Procedures (SOPs) and procedures the critical activities of clinical trials, thus ensuring that ICH-GCP and all applicable ethical and legal requirements are fulfilled. In collaboration with each partner institution, CRP will draft a quality manual for clinical research that must be reviewed and approved by the institution's AB. SOPs will be drafted and implemented, covering critical activities performed by each clinical research office. After SQIC is properly defined and implemented, healthcare professionals will be trained and those who are interested may become associated with the office.

1.2.2. CENTRO HOSPITALAR DE VILA NOVA DE GAIA/ESPINHO

"*Centro Hospitalar de Vila Nova de Gaia/Espinho*" was the first hospital in which I developed my internship. It is an institution that serves a big area of influence (covering about700.000 inhabitants), reason why it has a great potential for investment in clinical research (6). The hospital has three units, each one functioning in a different building. The unit I of the hospital operates in the old facilities of a sanatorium constructed in the beginning of the XX century, when tuberculosis became a big threat for Portuguese people. Some years later, health priorities changed and the sanatorium was converted to a central hospital – "*Hospital Eduardo Santos Silva*". CHVNG/E was the trail-blazer for pneumology and pulmonary surgery in Portugal, and it still keeps this therapeutic orientation. Later on, there was a redesign of the national health system that created "*Centro Hospitalar de Vila Nova de Gaia/Espinho*" by joining together this facility with two others: "*Hospital Distrital de Gaia*", which is now the unit II of CHVNG/E, and "*Hospital Nossa Senhora da Ajuda de Espinho*", which is unit III(6). These three units are shown in Figure 3.

Currently, most of the medical specialties are located in unit I, including the emergency room. I spent most of the time of my internship in unit I, as it was the location of our Clinical Research Office.

Unit II serves the departments of orthopaedics, maternal and child specialities (departments of gynaecology/obstetrics, paediatrics, neonatology and paediatric surgery), and the assisted reproduction centre, pre-natal diagnosis and a supportive operatory room.

Unit III has the ambulatory surgery department and the unit of palliative care.

CHVNG/E is an institution with potential to perform more and better clinical research. It is focused on the training of health professionals and on providing specialized, high-quality healthcare. Promoting innovation and playing a role in the development of new solutions for disease is mentioned in the hospital's vision(6). Besides, the AB recognizes how important clinical research

is as a strategy to improve the general training and the treatment options provided to patients(5). The greatest attractiveness factor is still the large amount of patients served by this institution, leading to a large pool from where possible patients can be recruited for clinical trials.

Figure 3 The three units of CHVNG/E: unit I on the left, unit II in the middle, unit III on the right.(6)

1.2.3. HOSPITAL GARCIA DE ORTA

"*Hospital Garcia de Orta, E.P.E.*" (Figure 4) was created in 1991 due to a population increase in the area, which the existent hospitals could no longer address. It is located nearby Lisbon, and it was the first institution in the southern margin of Tagus River to be classified as a central hospital, in 2003. This hospital serves a population of 350 thousand inhabitants in the areas of Almada, Sesimbra and Seixal, plus all the Setubal peninsula in neonatology and neurosurgery. Through the years there were new services being created, such as renal transplant and the intervention cardiology unit.

The hospital's vision is to become the reference hospital in the Setubal peninsula and in all southern Portugal for some therapeutic areas. The hospital's mission is to provide specialised healthcare to the population, and to develop training and research activities.

HGO is accredited by CHKS (Caspe Healthcare Knowledge Systems) in pathologic anatomy, operatory room, sterilisation, logistic management, imuno -haemotherapy, and clinical pathology.

Figure 4 "Hospital Garcia de Orta, E.P.E." (7)

This hospital is known by the quality of training of healthcare professionals, and considers clinical research as highly important in their development strategy.

1.3. REPORT STRUCTURE

This report is structured in five chapters. The first is this one, defining the general scope of the internship, preliminary training objectives and the description of the host institution. The second chapter describes the current state-of-the-art of clinical research, contextualising the reader in the field by describing what is clinical research and which types of studies are considered, and it also describes the ethical and regulatory context, what new paradigms of research are emerging, an provides an overview of distribution in the world and in Portugal. In chapter three are described all the activities I developed during the internship regarding clinical trials and also activities related to the hospitals' integration with Blueclinical and on-the-job training. Chapter four is the discussion and provides a more personal review of the internship, regarding objectives accomplished, differences between the two hospitals and the main difficulties I felt. Chapter five is my conclusion.

2. CLINICAL RESEARCH STATE OF THE ART

Clinical research is basically defined by the National Institutes of Health (8) as any research involving living human subjects. It is concretised in the conduction of clinical trials (interventional research with medicines or medical devices) and observational studies (non-interventional studies, evaluating normal clinical practice). The ICH-GCP, one of the most important documents in this area, define a clinical trial or study as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy"(9, p3).

Clinical research may address the study of mechanisms of disease, new therapies, interventions or technologies for disease, epidemiological studies and also studies of behaviour and outcomes (8).

Clinical research is the critical part of clinical development, which is the whole process since a new molecule is discovered until it turns into a new medicinal product or medical device getting marketing approval. The purpose of development is to discover if the new drug can be safe and effective in a specific dose range and schedule, and to establish a benefit-risk relationship that must be acceptable in order for the drug to be approved (10). The first step is the discovery of a new molecule with therapeutic potential from basic research. That molecule is called the "lead" and must then be developed in order to enter pre-clinical evaluation. After being studied in *in vitro* and in animal models, clinical development requires a determined set of clinical trials, which can be categorised in four different phases. Traditionally, these were sequentially named phase I, II, III and IV. A molecule must only step through one phase to another by proving its benefit in each phase. Nowadays, the terms "Human pharmacology studies", "Therapeutic exploratory studies", "Therapeutic confirmatory studies", and "Therapeutic use studies" are considered more accurate. In general terms, they would be a match, although this change happened because phases don't necessary have to be sequential, as explained in Figure 5 (11).

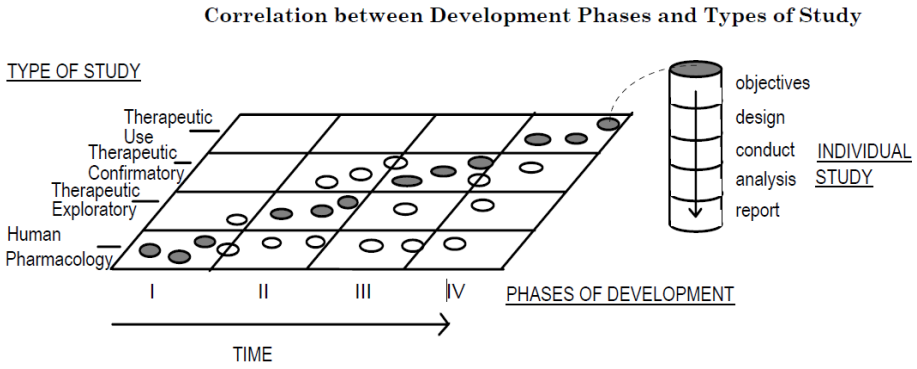

Figure 5 Correlation between development phases and types of study (11)

The objectives and examples of each type of study is the following:

- Human pharmacology studies (Phase I): These are performed in healthy volunteers or in selected populations of patients. These studies are the most controlled, and those in which inclusion criteria are stricter, because there is usually very limited information available on the molecule (12). They include first-in-men studies, designed to assess tolerance and identify the maximum tolerated dose, to determine Pharmacokinetic (PK) and Pharmacodynamic (PD) profiles in humans, to explore metabolism and drug interactions, and to estimate activity (11).
- Therapeutic exploratory studies (Phase II): The most important exploratory studies are those concerning Proof of concept". As the name states, the purpose of these studies is to prove that the drug does what it is supposed to. They are performed in small populations of target patients (12). Objectives include exploring the use in the targeted indication, estimate dosage and provide support for confirmatory studies (11).
- Therapeutic confirmatory studies (Phase III): Confirmatory studies aim to confirm the effectiveness of the drug when used in more similar conditions to daily practice. A large number of patients is included, as these studies will provide the benefit/risk relationship to support regulatory approval, and so they must be close to the "reality" (12). Their purpose is to confirm efficacy, establish safety profiles and dose-response relationships (11).
- Therapeutic Use (Phase IV): These are conducted when the drug is already on the market. "Post approval" studies aim to gather additional information about the drug usage in real-life conditions. Because they reach to a large number of patients, they allow identification of less common adverse reactions, and thus a redefinition of benefit/risk relationship and dosing recommendations (11). They may also study pharmacoeconomy, or pursue a safety purpose by addressing pharmacovigilance (12).

Besides clinical trials, which consist in interventional research, there are also observational studies. This type of research is non-interventional, meaning that the study does not interfere with normal clinical practices and conditions. Observational studies can be categorized in four types (13):

- Ecological- The "unit" studied is the group instead of the individual (e.g. relation of fat intake to risk of cancer, per country).
- Cross-sectional - A study that describes a specific time point, as in a snapshot. The exposure and the outcome are measured simultaneously. They are mostly used to study prevalence (14).
- Case-control - Two groups are chosen: one group of patients and other group of people without the disease. Then predictor variables are evaluated, such as exposure to risk factors.
- Cohort- Subjects are followed up over a time frame. The cohort starts with a sample of exposed and not exposed individuals, and over the course of time it evaluates the development of an outcome (e.g., disease progression)(14). They can be prospective, when exposure to risk factor and outcome both occur after the study initiation; or retrospective, when both exposure and outcome occurred prior to the study.

Clinical research and the overall drug development process can be highly demanding and complex. In order to achieve success, every one of the stakeholders must be engaged in the process (Figure 6).

The sponsor is normally the pharmaceutical company, but can also be an individual or an institution, which takes the responsibility for initiating, managing and/or financing a clinical trial (9). The clinical trial site is the location where the trial is conducted: it is usually a Hospital but can also be laboratory or other facilities. A CRO is an organisation contracted by the sponsor to perform one or more of the sponsor's functions and duties in a clinical trial (9). They can be delegated all development activities or just a part. The research team is the group of people that contribute to the conduction of the trial in a site: the responsible physician is the Principal Investigator (PI), which leads the rest of the team. The other physicians are named sub-investigators or co-investigators. Team is also constituted by nurses, pharmacists and maybe administrative or laboratory personnel (15). Regulatory Authorities are bodies with the power to regulate and inspect. In Portugal, the regulatory authority is INFARMED ("*Autoridade Nacional do Medicamento e Produtos de Saúde, IP*"), which authorizes the conduction of the trial, CEIC *("Comissão de Ética para a Investigação Clínica*"), which must give a favourable opinion, and CNPD ("*Comissão Nacional de Proteção de Dados*"), which authorizes the disclosure of the data involved in a clinical trial. Subjects are all individuals which provide inform consent and

participate in a clinical trial. They may be patients or healthy volunteers. Hospital ABs are also a stakeholder because they must review a financial contract for each trial to be conduct in their facilities and provide approval.

Figure 6 The main stakeholders in a clinical trial (15) **- adapted.**

From the site's point of view, a clinical trial is constituted by sequential phases of implementation and conduction. The first step occurs when a new trial proposal arrives to the site. That is called a feasibility assessment: when the sponsor has a new clinical trial designed and plans to implement it in various research centres, they perform a feasibility study in order to select which centres will perform the trial. It consists in a questionnaire that is sent to the sites to collect information about the staff availability, facilities and logistics, administrative constrains, and more specifically about the medical experience in the therapeutic area, number of patients treated at the site and how many patients would the site be able to recruit. The answers are then returned to the sponsor. After the sponsor receives several feasibility questionnaires, they will perform a pre-selection of sites, based on the answers given by each one, and then contact those of their choice. Then, a qualification visit (or Site Selection Visit – SSV) is arranged between the sponsor and the site, in which a representative of the sponsor that comes to the hospital and meets with the PI and its team, and checks the conditions of the site (ex. pharmacy, equipment, experience, motivation, etc.). By the

ICH-GCP, an investigator must be "qualified by training and experience" to perform a clinical trial, and it must have adequate resources available (9).

If the site is selected, the negotiation of the financial contract and submission process can occur. At first, the sponsor submits the study to INFARMED, CEIC and CNPD, and then it submits to the hospital's AB and local ethics committee when applicable.

After approval or even during the process, the sponsor organises investigator meetings. The purpose of these meetings is to present the investigational plan to the teams and explain specific details in order to promote the trial's success. There can be also investigator meetings later on, when the trial is already happening.

After all approvals are collected, trial initiation can begin. A site initiation visit (SIV) is scheduled, in which the CRA trains the team in the trial procedures, and responsibilities are delegated through team members. When everything is set up, it is time to recruit patients and make all the effort of submission worth it. Enrolling patients is the ultimate goal for everyone involved in a trial. Patients will provide the data for the study to be conclusive, which will lead to the sponsor paying to the site, thus motivating the team. Besides, as working for a company which is external to the hospitals and surviving out of clinical trial payments, enrolling patients is the key to success.

After a patient is included, there are sequential patient visits with procedures that vary according to the protocol. Although, some of them are common: the patient must always sign the informed consent form (ICF) before entering the trial; there are always IVRS (*Interactive Voice Response Systems*) or IWRS (*Interactive Web Response Systems*) systems to allocate medication, blood and urine samples to manage and send, among other tasks I will further describe in section 3.

In the end, when all patients complete or discontinue the study, and when the sponsor considers, there will be a close-out visit where the dossiers are closed and can no longer be changed. The management of these activities on daily basis is focused on section 3.

2.1. APPLICABLE ETHICAL AND REGULATORY CONTEXT

Presently, there are various laws and regulations applicable to clinical research. In its core, clinical research equals human experimentation: if used in its best potential it can bring huge benefits in health, science and knowledge, if used improperly it can lead to people being treated like guinea pigs in the most outrageous ethical conditions (16). The first flagrant example were the Nuremberg trials, when Nazi doctors coerced the prisoners in concentration camps into their hazardous experiments without any type of consent. Following this, the Nuremberg code was created in 1947, being the first code for protecting human subject in clinical trials. Based on the same facts, the Declaration of Helsinki was created and adopted in 1964, protecting the subject's rights in clinical

trials and stating that the interests of the subject must always prevail over the interests of science (17). Since the original version, it was updated several times, being the most recent version from October 2013.

As ethical concerns in clinical research were addressed, regulatory systems in different countries became to reflect them as mandatory principles. In Europe, regulatory harmonisation of the clinical trials and approval systems remotes to the creation of the common market with the treaty of Rome. In the European Union (EU), laws assume the form of directives, regulations, guidelines, and other opinion papers and recommendations. These documents differ in scope and applicability: regulations overrule national laws and have immediate application in the community countries; directives must be transposed to the national law of each country; guidelines are published by scientific committees with no legally binding value, although they are an official reference. In medicines regulation, directives are adopted by the 27 Member States plus 3 countries from the European Economic Area: Iceland, Lichtenstein and Norway (18). All regulations and guidelines applicable to pharmaceuticals are collected in 10 volumes of "The Rules governing medicinal products in the European Union", also known as Eudralex (18).

Following the success harmonisation in the EU, regulatory authorities from Europe, the United States of America and Japan wished to expand harmonisation trough these three regions. In 1990, it was created the ICH – "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". The ICH developed tripartite guidelines covering the main focus topics for developing new drugs: efficacy, safety and quality. This harmonisation resulted in a great benefit: as the regulatory requirements are the same, industry needed to perform less testing; as drug application forms are similar, regulatory assessment became easier; and industry could shift its focus into innovation instead of spending resources in bureaucracy. Drug development was fastened, whilst safeguarding the issues about safety, quality and efficacy (19).

One of the guidelines provided by the ICH, the E6 or "Guideline for Good Clinical Practice" (ICH-GCP) (9) is considered an international quality standard when it comes to clinical trials involving human subjects. It stands the principles for design, conduct, record and report of trials. Compliance with ICH-GCP assures that the rights, safety and well-being of the subjects are protected, and clinical trial data are quality and credible. These principles are consistent with the ones in the Declaration of Helsinki, and thus will ease the acceptance of data to support regulatory approval in the ICH regions.

ICH-GCP defines as pillars that a trial must be scientifically sound, described in a detailed protocol, and should only begin after a foreseeable risk/benefit relationship is defined based on the available information from pre-clinical and other clinical trials. The rights and safety of the subject

also prevail over other interests, and each subject must give informed consent before entering the trial. All information is confidential, respecting the subject's privacy. The trial must be conducted according to the protocol, and information must be dealt with in a way that allows accurate reporting, interpretation and verification (9).

The responsible authority for evaluating medicines it the EU is the EMA (European Medicines Agency). In was created in 1995, with the aim to ensure the protection and promotion of public and animal health (20). It uses resources from all the Member-States and coordinates them for the evaluation, supervision and pharmacovigilance of pharmacovigilance of medicinal products (18).

Regarding current regulatory practice in the EU, "Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" is the most important and it is known as "The clinical trials directive". It states the requirements for conducting clinical trials in the EU, and outside if the drug intents to be marketed in the EU (21). All the ongoing or completed trials within the scope of this directive are contained in EudraCT, a large European database that provides the authorities with the necessary information to communicate and oversee clinical trials and drug development (21).

This directive was further concretised in the "Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products", known as the ICH-GCP Directive (22).

In Portugal, 2001/20/EC was transposed into decree-law 46/2004, of August 19th. In April 16, 2014, a new clinical research law was published – Law 21/2014 – replacing law 46/2004 and incorporating dispositions for trials with medical devices (23).

Despite being a regulatory pillar for medicines development in Europe, Directive 2001/20/EC was much criticised, as it somehow hindered the clinical research activity instead of promoting it. To increase European competitiveness in the field, a new European regulation was proposed on July 17, 2012: "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" (24). This will replace directive 2001/20/EC, and by assuming the form of a regulation its application will be equal throughout the European countries (thereby reducing differences in transposition for local languages which led to divergences with 2001/20/EC). The proposal redefines the concept of clinical trial and clinical study, simplifies the approval submission when the risk from the IMP (Investigational Medicinal Product) is considered low, states new authorisation procedures, new

ways of reporting safety information, and introduces an EU Portal through which trial data and information will be introduced and store in the EU database. The proposal for regulation is expected to be in practice in 2016 (24).

2.2. CLINICAL RESEARCH WORLDWIDE

The locations with more tradition in clinical trials are North America, Western Europe and Oceania. Regarding the number of trial sites (centres where the research is performed), the United States of America lead with eight times more sites than the following Germany. Together, traditional regions comprise 66% of the global trial sites.(25)

Figure 7 represents, per country, which recruit more patients into clinical trials. North America has the higher values, followed by Europe and Oceania, which supports the previous information.

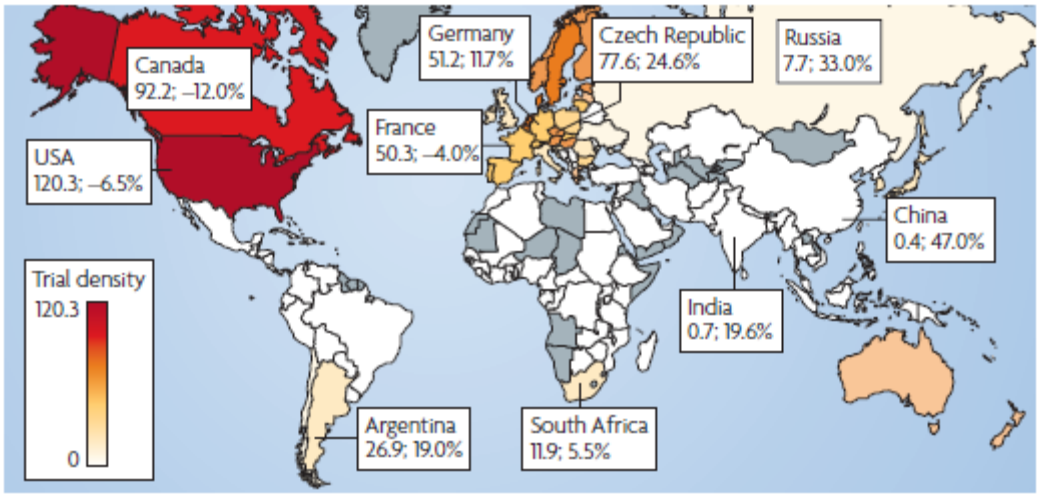

Figure 7 Density of recruiting sites, per country inhabitant (2005). (25)

The largest database concerning clinical research worldwide is ClinicalTrials.gov: a registry held by the United States National Institutes of Health. This registry lists and describes most clinical trials occurring worldwide, thus allowing more detailed assessments on the subject. Actually, there are 167456 studies registered on this platform, of which 85193 are in North America, 46440 in Europe, and 4482 in Oceania.(26).

Nowadays, we are facing a shift to the "emerging regions", namely Eastern Europe, Latin America and Asia. Although they lack tradition in clinical research, they offer conditions which are hard to compete with: lower operational costs, while still recruiting large numbers of patient very quickly. Besides, globalization of CROs, harmonization of guidelines and regulatory authorities from these emerging countries are enhancing this shift.(25) Due to lower need of investment, this countries are expected to grow even more in this field.

The proportion of trials of each phase per region is not equalitarian either: North America has a very high proportion of early-phase trials, and in Europe, Latin America and Asia there is a much higher proportion of late-phase and confirmatory trials(25).

Globalization in clinical research can be addressed by two sides of the same coin: in one hand, it helps spreading medical knowledge and practice, and patients gain access to new therapies; on the other hand, regulatory supervision may not yet be adequate so there are some concerns with ethical issues and scientific conclusions drawn from the studies(25).

Regarding worldwide investment and support context for clinical research, the situation is favourable (Figure 8). After the first market contraction in expenditure with pharmaceutical R&D of 2009, the market is forecast to slowly grow at 2,3% a year until 2016 (27). It is a slow growth, in which phase III trials will still dominate the market.

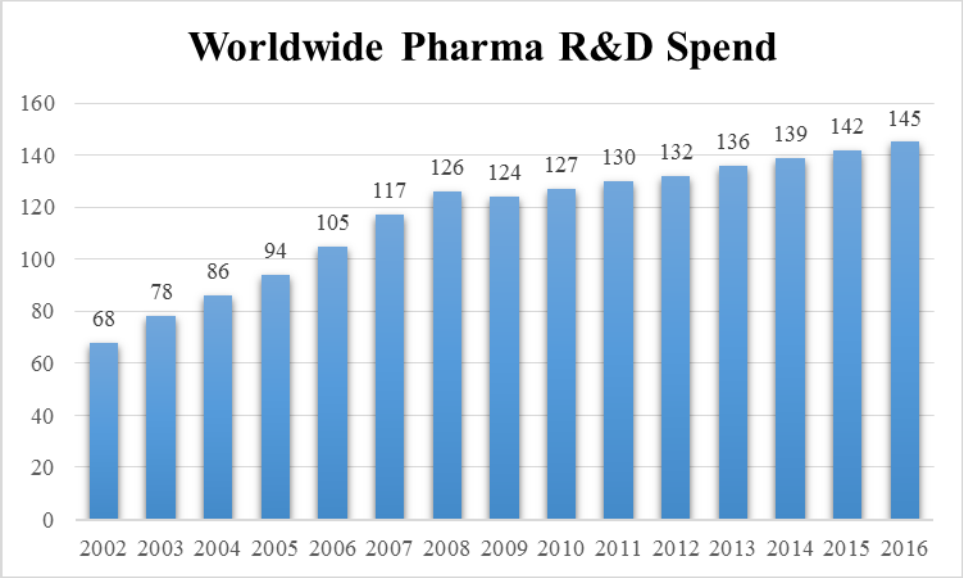

Figure 8 Worldwide Pharma R&D Spend Forecast (billion dollars) – adapted (27)

2.3. A NEW RESEARCH PARADIGM

As the world life expectancy rises, populations become older and more demanding for new and better medicines. Until now, drugs have been developed through the "old" development model, but it is facing some serious challenges as these new demands emerge. This traditional model for drug development follows the model represented in Figure 9.

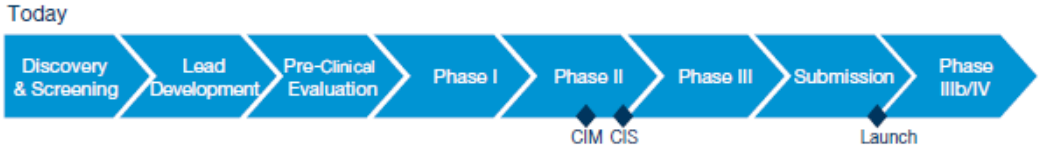

Figure 9 The traditional drug development model. (28) **CIM – Confidence in Mechanism; CIS – Confidence in Safety**

A new "lead" compound (meaning a compound with potential to be developed) may be discovered through the most various ways: screening of natural products, synthetic design to match a certain target protein, computer-aided search in structural databases, or even by serendipity (29). After discovery, the lead must be further developed in order to enhance its chemical and pharmacological properties. In this phase the molecule is patented, and then starts the pre-clinical (also called "non-clinical") development (30).

Pre-clinical testing is performed in vitro or in animals, with the purpose of identifying early pharmacokinetic (PK) and pharmacodynamic (PD) properties, and understanding the toxicological profile of the new drug (establishing minimum and maximum dose ranges, defining toxicology and establishing an initial safe dose to test in humans). Data must be transposable to humans by extrapolation (30).

Traditionally, developing a new drug takes in average 12 to 14 years. After new molecules are discovered and identified as potential medicines, then follows pre-clinical and clinical evaluation (which takes most of the development time), and only after that the drug is approved and marketed. With this model, companies start investigating too many new molecules too early, which causes a molecular fallout: most of them fail after too much money had already been spent (28). This leads to a big productivity crisis in pharmaceutical companies. Comparing with two decades ago, companies now actually invest more in R&D activities and produce less molecules. Discovery of new molecules has not decreased; it actually increased due to development of the genomics, metabolomics and proteomics that followed the sequencing of the human genome. So, a new model was created to accompany the speed of discovery and face the new market needs (Figure 10).

The new development model is focused on selecting candidates earlier in the development process, thus saving time and money. Facing the abundance of drug discovery, companies must have a clear scene of the pathology they are addressing and the involved mechanisms of physiologic response. After that, proof of concept should be obtained as early as possible, by testing whether or not the molecule works the way it is supposed to. Here is where most molecules should fail, and only the ones whose concept is proven must advance to further clinical development.

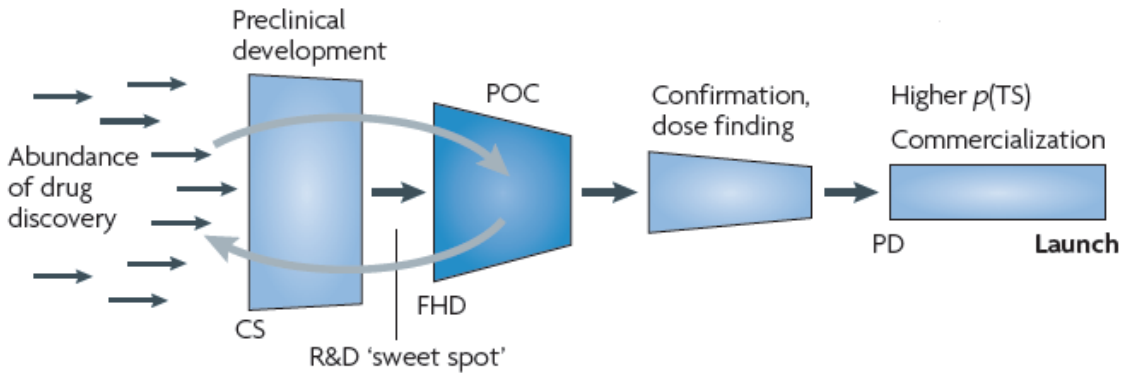

Figure 10 "The quick win, fast fail drug development paradigm" (31)

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

Because it supports earlier understanding of disease pathophysiology, this model enables earlier testing for biomarkers, determining subsets of patients which may respond differently to different drugs, thus supporting the future reality of personalized medicine (31).

Both in Europe and the USA, there are governmental initiatives supporting the implementation of new paradigms. In Europe it is the IMI - Innovative Medicines Initiative, and in the USA the CPI - Critical Path Initiative. They both aim to improve and speed up the processes trough drugs are developed, evaluated and manufactured, by supporting innovative research projects.

2.4. CLINICAL RESEARCH IN PORTUGAL

Data in clinicaltrials.gov shows that, from 46440 studies conducted in Europe, only 1052 happen in Portugal. In the map of Europe (Figure 11), it is possible to see that Portugal is still far behind from other western European countries when it comes to clinical trials. Especially comparing to Belgium, which is country approximately with the same size as Portugal, the number of trials is five times higher.

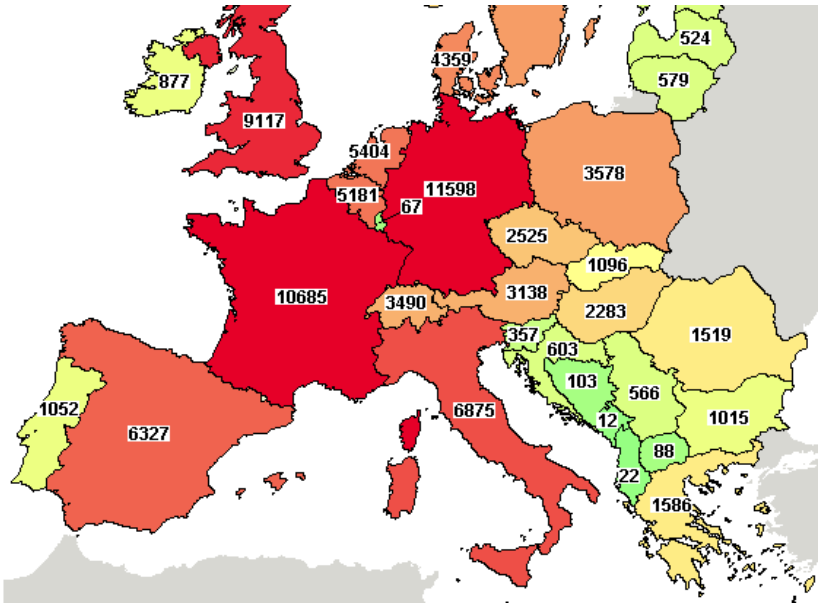

Figure 11 Map of all studies in ClinicalTrials.gov - Europe (26)

In Portugal, the number of submitted and authorised clinical trial applications has been decreasing, as shown in Figure 12. The historical lowest happened in 2011 with only 88 trials approved (32). This trend can only be reversed if something is done to address it. Otherwise Portugal will eventually vanish off the global panorama.

Most clinical trials in Portugal are phase III (68% of total in 2012), whilst phase I trials are residual. Therapeutic areas with more ongoing trials are oncology, nervous system and infectious diseases. Most clinical trials are international and supported by multinational R&D companies, and there are very few trials of the investigator's initiative. Approval times are very slow, especially if including the time taken by the hospital Abs. The three sponsor companies with more clinical assure 41% of the number of trials conducted (15).

Transposing these characteristics into economic value, it means that there is a huge potential slipping through our hands. Investment in the area by international pharmaceutical R&D companies reached 36 million euros, and each euro invested in clinical trials has a revenue of 1,98€. There are actually one thousand jobs created by clinical trials. The tendency to decrease activity in clinical research reveals a preoccupant loss of competitiveness, even more knowing that

if properly harnessed, the area could have a gigantic positive impact in the Portuguese economy (15).

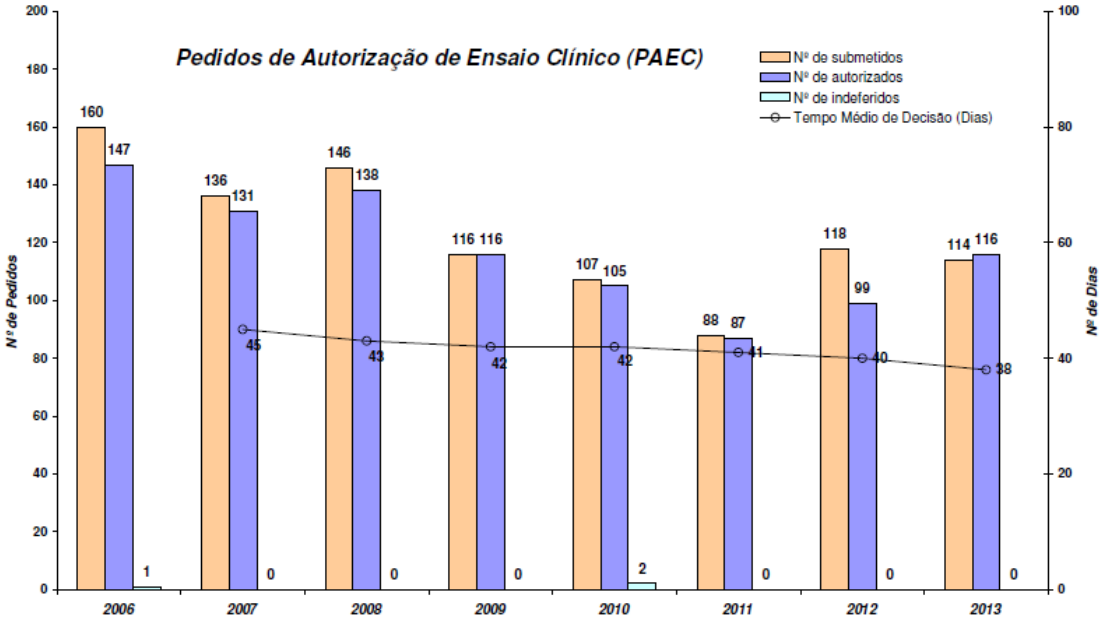

Figure 12 Number of submitted and authorized clinical trials by Infarmed, last updated on 31/01/2014. (32)

Posted this, what can be done to improve the representativeness of Portugal in clinical research? First, one must not face the context of crisis and negativism with hopelessness. Being in the bottom must be faced as an incredible opportunity to grow (33). The study of 2013 from the Portuguese association of the Pharmaceutical Industry (15) proposes three initiatives that could be practiced in order to enhance market development in this field: they state that the current legislation must be reviewed for reducing times between submission and beginning of recruitment, clinical trial sites must be capacitated, and there must be incitements to involve more investigators into research. In fact, once that pharmaceutical R&D is increasing in the rest of the world, Portugal has no reason to be left behind.

Portugal's political environment is supportive to the development of clinical research. Dr. Paulo Macedo, the Portuguese Minister of Health, publicly recognizes clinical trials as a new source of funding that might be exploited in order to adjust the health expenses whilst increasing the access of the population to new medicines and interventions. With the recent approval of a new clinical trials law, he said that the goal was to "increase not only the number of clinical trials, but also their quality, their representativeness in terms on patients involved, and expand the number of phases" (34).

By investing more in clinical trials, Portugal can achieve better health indicators, early access to advanced treatments, better patient assistance, more scientific development, while creating jobs and reducing public expenses.

This is the context in which Blueclinical, Ltd is created.

3. EXPERIENCE AS A CLINICAL RESEARCH COORDINATOR

During the internship I worked as a clinical research coordinator in two different hospitals. Although the main functions dealing with clinical trials were very similar, the hospitals had very different contexts and integration of Blueclinical in the institution was performed differently. This chapter is subdivided in three subtopics, reflecting these aspects. First, I will describe clinical trial related activities in a sequential manner, which was similar in both hospitals, and then I will refer integration with CRP and office implementation differences, and finally I will focus on the training provided by Blueclinical during the internship.

My main responsibilities as a CRC were the following:

- Clinical Research coordination activities, according to applicable procedures, legislation and regulations, namely, ICH-GCP.
- Point of contact for sponsors, "bridging" their contact with all hospital departments.
- Collaboration in the development and implementation of the clinical research quality management system.
- Financial agreement revision and implementation.
- Collaboration in audit and inspection preparation activities and in the implementation of eventually necessary CAPA plans.

As CRC I must provide support to all hospital's departments and therapeutic areas, bridging them with the sponsors and with each other in what concerns clinical research. This includes not only clinical departments, but also supporting departments such as pharmacy, clinical pathology and AB.

3.1. CLINICAL TRIAL RELATED ACTIVITIES

3.1.1. FEASIBILITY

From what I experienced in the internship, a hospital can be contacted for a feasibility study directly from the sponsor or CRO, or from Blueclinical CRP's Back-Office.

In the first scenario, the sponsor/CRO sends an email that contains minimal information about the study, such as the title of the protocol, name of the active substance and disease concerned. This email also contains a CDA (Confidential Disclosure Agreement), and asks if there is interest in the hospital to pursue the study.

The person contacted may be a physician or some of the CRCs. When the email is addressed to the physician, that person will presumably be the PI; when it is the CRC and the sponsor/CRO do not refer a name, the CRC job is to contact the head of the respective department. He may himself by the PI or may refer a colleague's name.

If the PI has interest in the study, he must sign the CDA stating that he will not disclose any confidential information contained in the protocol synopsis and the questionnaire that will be sent afterwards. At this point, I would inform the back-office of CRP that a new proposal arrived, for them to ask the sponsor if they would be interested in expanding it to more sites from the CRP network.

The CRC sends the signed CDA to the sponsor/CRO and communicates that the PI is interested, and only after that the protocol synopsis and feasibility questionnaire are sent. This is the correct order of procedures, although I saw that sometimes the three documents came in the initial email to save time.

As physicians are most of the time very busy persons, my role after receiving further information was to study the synopsis (and also some concepts from the therapeutic area concerned), to be able to explain it to the doctor very briefly. After that, the questionnaire itself must be fulfilled.

There are online and paper feasibilities. Both of them are very extensive and time-consuming.

After realising that these questionnaires were similar to each other in many aspects, I started to read the questionnaire before the physician and answer the questions I knew by myself: which facilities and equipment are available, in what times does the ethics committee and the AB approve a trial, how many audits were and how many findings, and other administrative data. That being done, very few questions were left to the doctor: only those concerning medical issues such as current practices, how many patients exist with the pathology, how many does he expect to recruit to the trial, and what are the main expected constraints. This method changes his perception about how extensive the questionnaire is and how much I could help him.

What I realised trying to obtain accurate data about the number of patients with a certain pathology was that almost no department has databases of patients. Numbers answered in feasibilities were based mostly on assumptions, and so I usually advised doctors to underestimate the recruitment potential: it is better to have a small goal and achieve it than being too greedy and cause a bad impression in the end by recruiting less than expected.

After all questions are answered, I would send the questionnaire to the sponsor, by email or just my clicking a "submit" button. After that I would again inform back-office that the questionnaire has been submitted. Then we must only wait from some feedback from the sponsor (the back-office is responsible for the follow-up of this processes).

Regarding the feasibilities that come to the hospital through Blueclinical CRP's back-office, they can come already with a protocol or they can be proactive. Those who come with a protocol follow a similar scheme of those coming from the sponsor: there is an assessment of interest and a CDA that must be signed, and then there is a questionnaire to answer. The difference is that the site's point of contact is always the back-office instead of the sponsor. Proactive feasibilities come in the form of a few questions (e.g. number of patients treated of a certain disease, what is the standard treatment for that disease in the hospital, etc.) and a brief interest assessment before the study design is known.

When sponsors and CROs started contacting Blueclinical CRP for feasibility assessments directly, I noticed that sometimes there was duplication of entry points. Once, one of my colleague CRCs went to present the doctor the new study proposal coming from the back-office, and the physician already received it in his mailbox a few time ago. Most feasibilities come with a due date of one or two days to answer, which is very difficult for doctors since they are always on a busy schedule. When we arrive with these due dates and the doctor has already received the same feasibility before that may lead him to think we are being inefficient when that is not the situation.

3.1.2. SITE QUALIFICATION AND SELECTION

Answering a feasibility questionnaire may result in the site being selected or not to conduct the clinical trial. When the sponsor is deciding which sites to choose, they perform site selection or qualification visits to verify the conditions offered by the hospital, and whether or not the answers given on the questionnaire are true.

I was present in at least two SSVs, one in CHVNG/E and other in HGO. In one of them, the sponsor already knew the site conditions and staff, because they worked together in the past, and so the SSV was conducted as a formality. In the other one, the sponsor had no knowledge whatsoever about the concerned department, the PI or any other team member.

In a qualification visit, a sponsor or CRO representative comes to the hospital to assess the offered conditions. He will ask for the PI's training and previous experience with clinical research (how many trials he had participated and for which indications), and request his *Curriculum Vitae* (CV) and ICH-GCP training certificate. It is evaluated whether the hospital has availability to perform imaging procedures or they have to be outsourced, for example, whether the department nurses can perform infusions or it needs to be done by specialist nurses, or whether pathologic anatomy is able to provide historical biopsy samples. Availability of materials such as a centrifuge, a refrigerator or a -20ºC or -70ºC freezer is also assessed.

After the qualification visit, we must wait the answer from the sponsor on whether the hospital had or had not been selected to perform the trial.

During my internship, I noticed that most feasibilities that turn into a qualification visit resulted in the site being selected, except when the sponsor had chosen not to bring the trial to Portugal.
Before being the back-office to follow up sponsor feedback, it was the CRC's job to do that. In CHVNG/E, it was needed to "catch up" some feasibility processes which were lost and whose feedback was unknown. Our action was to call the sponsor and ask directly what happen with that specific trial. Sometimes, the sponsor had cancelled the trial globally, but the most common is trials getting "shuttled out" from Portugal and still happening in the other parts of the world. This was some evidence I saw of the premise of Portugal becoming slightly apart of the global panorama in clinical research.

3.1.3. BUDGET NEGOTIATION AND SUBMISSION PROCESS

In this section I will include all procedures since the sponsor informs the site that it has been selected through site activation. I performed several submission processes alone in CHVNG/E, but in HGO I did not have the opportunity to do so within the time frame of this report.
After receiving confirmation that our site was selected to a specific trial, I would start gathering the required documents and negotiation of financial contracts. In first place, the sponsor needs approval from INFARMED, CEIC and CNPD. For the initial submission, a set of documents are required from the site: the PI CV, protocol signature page signed by PI and declaration of facilities. GAGIC provided a template for CVs to be collected focusing previous experience in clinical trials and ICH-GCP training. Protocol signature page is provided by the sponsor. The declaration of facilities can be in a sponsor template, and this case there is one for the head of the department to sign and another one to the head of the pharmaceutical services. With GAGIC, we created a template of our own in which all authorisations are provided in one declaration only: it states the facilities, equipment and human resources available for the trial, and then all head of departments involved sign below in agreement. This way it is ensured that every required service was involved in the process since the beginning, and it spares one declaration. My job was to go to all the required departments, remember them about the study and the collect signatures. If the department agrees with the trial, its head would sign the declaration. If it does not, one of two things could happen: if it is key service like pharmacy the trial may not be able to proceed; if it is a complementary service like imaging these procedures can be performed in an external facility.
After several meetings between Blueclinical and CEIC, there are two documents that are also requested by CEIC in order to clarify the CRCs position in the hospital and ease the approval. One of them is for Blueclinical to authorise the participation of one or more CRCs in each trial, and the other one is for the president of the AB to sign with the same purposes. To avoid the congestion of

the AB, there is one document for the AB to sign that delegates this function to the office coordinator. I must provide these to the sponsor along with the initial "submission package".

After approval from INFARMED, CEIC and CNPD, or immediately after site selection (as the sponsor agrees) the submission process for the hospital can begin. In CHVNG/E there were verification lists of all the documents that must be included in the submission dossier to be approved by the AB. There was one for clinical trials (with medicinal products), one for clinical studies (with medical devices) and other for observational studies. The following tables describes the general structure of a submission dossier for a clinical trial:

Table 1 List of required documents in a submission dossier for a clinical trial

Title	**Description**
Cover Letter	A letter written in Portuguese, addressed to the AB, referring EudraCT number and protocol title and number, requesting approval of the trial. It must be signed by the sponsor.
Index	Identification of all documents, with version/date.
Contact List	Sponsor or CRO contacts.
Protocol	Updated version, signed by the sponsor and PI
Protocol Synopsis	In Portuguese
Site Facilities Declaration	A template provided by GAGIC describing all facilities, equipment and human resources available for the trial, and including the signed authorization of the head of all departments involved (e.g. Pneumology, Pharmacy, Imaging and pathology).
Investigational Product Circuit	Template provided by GAGIC; defining who is responsible for supply, reception, storage, prescription, preparation, dispense, administration and devolution of the IMP.
Principal Investigator's CV	In the GAGIC template.
Financial Agreement	At least two copies; sponsor's template until CRPs is not available, with the final result of negotiation.
Insurance Policy	
CEIC Approval	If applicable
INFARMED Approval	If applicable
CNPD approval	If applicable
Sponsor Declaration	When CEIC, INFARMED or CNPD approvals are not yet available, this declaration states that the sponsor will not initiate the trial before this approvals are collected.

The investigational product circuit and medication feasibility declaration are two templates which needed to be completed in the submission phase. They basically stated what are the IMPs involved

in the trial and who are the responsible persons/services for handling them (supply, reception, storage, prescription, preparation, dispense, administration and devolution).

At this phase, the PI must define the investigation team for the trial: who will be the responsible co-investigators, nurses, pharmacists and study coordinators, and must attribute a defined percentage to be in the financial protocol destined to each one. As in this case CRCs are paid by Blueclinical, they cannot receive a percentage and must appear on the division as receiving 0%.

One of the most important things in this phase is the negotiation of the financial protocol. In the first times I did this, I would receive a previously drafted contract from the sponsor. Then I read the document and checked with the protocol if every procedure is contemplated and if the value is in accordance. To check payment per procedure was really time-consuming but it was an objective task that I could achieve. To assess if each procedure was being underpaid was tougher. I was provided with big tables of standard values for some procedures that I could use as comparison. Although, some procedures had an established value as a pack (e.g. height, weight and vital signs) and the protocol only required a part of that; other procedures were not contemplated at all. Another way of doing this was to estimate the time the doctor or the nurse would require to do the procedure and pay it according to their salary per hour, but I found this very uncertain.

Negotiating financial contracts was for me a very difficult task at the beginning, because I lacked knowledge on this field. I was able most of the times to estimate if the amount was or not fair. Nonetheless, when I found a trial to be underpaid, I felt like I could not request a higher payment because there was no solid support behind my request. All negotiation of financial contracts is now centralised in the back-office, which is for me a "relief". In that way I know that the person responsible can certainly do a better job than I did, and that will save time for ongoing clinical trials and recruitment.

3.1.4. INVESTIGATOR MEETINGS

During the internship, I had the opportunity to attend two investigator meetings. The first meeting I attended was in Coimbra, Portugal. It was organised by Boehringer-Ingelheim for the trial 1200.55, relating to a new molecule developed to treat lung cancer. The second one was in Barcelona, Spain, organized by AstraZeneca for the SELECT-1 study, also in the therapeutic area of lung cancer.

In investigator meetings, the trial is presented by the people that are directly involved in its conception. This is great because they have more insight in the trial than CRAs do, and they are speaking for a large number of site personnel. So, they can make the correct information reach a high number of sites, as they are also more prompt to answer specific questions.

In both meetings, I had the opportunity to meet investigators and study coordinators from other sites and other countries. I sat next to the other Portuguese people, due to ease of communication, and I actually enjoyed getting to know those from other sites doing the same as I do while discussing the themes being presented. After attending an investigator meeting, I realised that I knew more about the concerned trial when comparing to others I only got on-site training.

3.1.5. CLINICAL TRIAL INITIATION

After all approvals are gathered, it is time to prepare initiation. The sponsor will send us links to perform e-learning trainings (in general subjects as ICH-GCP, and in trial specific subjects). After those trainings are complete the IVRS or IWRS systems are activated and each team member receives login credentials. The same happens with CRF systems. The sponsor triggers the dispatch of trial materials such as medication and collection kits that will arrive to the site in this phase.

In the beginning of my internship, in CHVNG/E, I would create flowcharts summarizing the procedures to perform before, during and after each patient visit. This was a nice exercise for me to learn more about the procedures, although this was very time-consuming and later on I stopped creating flowcharts. Nevertheless, we continued creating preparations for each visit with the topics that must be written in the patient file.

In HGO, there is fewer time available, and no checklists were created.

A SIV is scheduled, in which a sponsor or CRO representative comes to the site to train the team in a more personal approach (as they already did the e-learning trainings). I was present in three SIVs. These are useful to resolve any doubts we may have and to get to know the protocol with more detail and in a more adapted approach to the hospital's reality. This is when the responsibilities of each team member are defined and the delegation log is fulfilled and signed by the team members and the PI. As the team is gathered, the SIV is a great opportunity to manage pending issues such as the collection of the team CVs.

After the team completes all trainings, all materials arrived to the site and everything is ready to start recruiting patients, the sponsor activates the site. We receive an email stating that and we can indeed start recruitment.

3.1.6. RECRUITMENT STRATEGIES

By seeing the reality of recruitment in two different hospitals, I have two different views on recruitment strategies.

In CHVNG/E, especially in the oncologic pneumology department, our main recruitment tool were the "group meetings". These meetings happened every Monday morning, and all physicians of the

department were gathered to discuss their medical cases, irrespective of clinical trials. One of the four CRCs would always be present in each meeting. Our role was to be there for the whole meeting paying attention to the patient characteristics, and constantly comparing them to inclusion and exclusion criteria of the open trials in order to alert the doctors when an eligible patients comes up. This strategy was not always efficient. It is hard to understand everything said by the doctors without losing the track, because they know their patients and most of the times do not list all the criteria we need to know. Said that, the result of many group meetings was zero patients recruited versus a lost morning with other work left to be done. By the time we realised that group meetings were not such a good strategy, we started reading on Fridays all the patient files that were to be discussed in the next meeting. That was a better strategy in the aspect that we could be more focused on the criteria for entering each trial. Although we noticed that the doctors did not pay much attention to our notes in the Monday, and we needed to remind them anyway. In the internal medicine department, one PI provided us with a big list of patients followed there for us to help identifying patients. It is difficult to ascertain all criteria just from searching in the hospital's informatics systems. Overall, I saw recruitment goals as a statistic number that may or may not be achieved.

When I arrived to HGO, I faced a completely different situation about recruitment. At first, I realised that doctors would become upset and frustrated if they are unable to achieve recruitment goals. They take that number as a personal commitment and engage to pursue it. Recruitment strategies also vary from department to department. In Cardiology, I noticed that my colleague had a good relationship with the doctors and they were able to talk more openly about everything, including obviously clinical trials and including patients. She worked most of the time in a meeting room of their department, which contributed to the good relationship created, and which allows a huge proximity to all staff and to the patients. In the two clinical trials with more success in recruitment, patients should be hospitalized at screening. Hospitalisation ward of cardiology is physically really close to that room, and so there is a high level of proximity with all intervenient in recruitment. She would know the conditions of patients in there and if one could be included, she would go to the responsible doctor and ask if inclusion in the trial could be considered for the benefit of the patient. These clinical trials in Cardiology have wide inclusion criteria. This is not the only reason, but in other services the recruitment is not so high. When patients must be recruited from outpatient visits, the job is a little harder. Only doctors know their patients, and so it is more difficult for us to help. Strategies here could be similar to those used in CHVNG/E. What I noticed was that doctors have more motivation to recruit and to achieve recruitment goals.

One effective method is to establish a recruitment plan prior to the trial initiation, defining what strategies will be used to recruit patients. That would ease the process during the trial and speed up recruitment.
Patients spotted using these strategies are considered “identified”.

3.1.7. TRIAL SPECIFIC PROCEDURES

After a patient is identified, a screening visit is appointed. Each protocol is different from the next one, although some things are common. I will only focus the common procedures.

INFORMED CONSENT

In the screening visit, the first procedure is always to explain the study to the patient in terms he can understand. It is usually the doctor who explains this, although sometimes I was there too to help clarifying the information. The ICF is useful to guide the explanation. This explanation is supposed to be a discussion with the patient and he should be encourage to ask any questions he may have. I have seen patient react very differently when we propose them a study: some patients are very submissive to the doctor opinion and often say “If you say so, doctor, than I will do whatever you find the best for me”; other patients hear the word study and immediately start picture themselves as guinea pigs and will not enter the study, even if we clarify the conditions and safety requirements of studies. I have seen patients making up excuses not to be available for the appointments when in fact they are scared, I have seen wives not letting their husbands participate, I have seen patients who are just afraid of needles, and I have even seen patients who did not enter a study because their family doctor told them not to. One thing I realised was that the most confident the doctor is with the trial and explaining it to the patient, higher is the probability that he accepts. And if the doctor is not comfortable, it is our job to “train” him so the next time he will be.
After the explanation, if the patient agrees to participate, we provide him two copies of the ICF for him to sign. Both should also be signed by the responsible investigator. One copy is to be archived in the patient file, and the other one must be kept with the patient. Only after this step is complete we can proceed to the visit specific procedures.

SCHEDULE OF ASSESSMENTS

Each protocol defines a specific set of assessments to be performed at each visit. According to the therapeutic area there could be more or less procedures, such as spirometries, electrocardiograms (ECGs), quality of life questionnaires, among others. Although, some of them are standard and

must be performed in almost every visit, including a set of assessments for the nurses, other for the doctor, and other for technicians when applicable.

The procedures for nurses are usually the measurement of vital signs, height and weight, collection of blood samples, and when applicable to train the patient with self-injectors or other devices. From what I saw, all these procedures are normally to be performed before the medical examination of the patient. In CHVNG/E there were also the nurses who got the patients to answer the questionnaires.

After that, the patient is seen by the doctor, which performs his usual evaluation plus the procedures required by the protocol.

If the protocol requires imaging procedures, those should be scheduled by the CRC according to the timings defined in the protocol.

In the two hospitals, patient visit scheduling and appointment was performed differently. In CHVNG/E, the patient appointments were schedule as any other patient; when he arrived, he must wait for its turn, then go the nurses room. After that, he would wait for the local lab results to be available if needed, and only after that he is seen by the doctor. This method seems logical, but many times it made me wait a lot of time and keep asking the secretary about how much time was it left to the appointment. In HGO, patient visits are scheduled by the CRC only, according to the doctor's availability. When the patient arrives, it is the CRC that would receive him and ask how he has been feeling, and then guides him to the nursing room and gets the doctor to come see the patient. Although, it is important not to forget that this comparison is between two different therapeutic areas and not all approaches are transposable.

IXRS SYSTEMS

In every visit, I or any of my colleagues must contact IXRS, meaning it can be IVRS – by phone, or IWRS – via web. These systems allow the registration of the patient status in every visit and the allocation of blinded medication. Contacting IXRS every time is always similar: whether I must dial a phone number of enter a website, I will be prompted to confirm the patient number, date of birth, confirm the visit number and if there is any medication to be dispensed. After that, the system provides the medication codes that must be dispensed and sends a confirmation e-mail to the team that must be filed in the patient file. Medication codes must be written in a prescription sheet that would be taken to the pharmacy to retrieve the medication itself.

Although this seems like a linear procedure, there were differences between the two hospitals. In CHVNG/E, I would only contact the system after the doctor already examined the patient and confirmed he must proceed to the next visit. After the appointment, I would get to the pharmacy as fast as I could because the patient was in the hospital just waiting for me to come with the IMP so

he could leave. In HGO, as the CRCs are the first persons to check on the patient, we would contact IXRS and get the medication while the patient is in the nursing room or waiting for the doctor. Of course we only did this if the patient seemed healthy and without complaints, depending on the disease considered (in oncology, the doctor always examines the patient before IXRS is contacted). The method used in HGO results in a faster visit, allowing for more visits to be performed in the same day. If there are more than one patient in the same department in the same morning, in CHVNG/E they would be attended sequentially, and in HGO they would both start by nursing procedures, the CRC would contact IXRS and bring medication for both, and then the doctor (if it is the same) examines both of them sequentially.

BIOLOGICAL SAMPLES PROCESSING

Blood and urine samples must be collected in almost every visit. Per protocol, they could be analysed in the hospital's local laboratory or in the sponsor's or CRO central laboratory (or both). For central laboratory analysis, the blood is drawn into specific collection tubes that comes into small boxes called "kits". These kits also include transfer tubes, to where the blood plasma must be transferred after the sample is centrifuged, and the requisition that must accompany the samples when they are sent to the central lab via courier.

In CHVNG/E I never processed any patient samples. This was done by the nurses in oncologic pneumology department, or by the clinical pathology department. In HGO I processed samples almost every day, and I found out I actually liked doing it. For each protocol there is an associated lab manual describing what needs to be done and it is not hard to follow. Most samples need to be centrifuged, but others do not. Sometimes I was required to perform blood smears, which was quite a challenge at the beginning because I could not get them right. After all samples were properly separated and identified, they are put into specimen transport bags to be sent to the central lab. They can be sent at ambient temperature, refrigerated with frozen packs, or frozen in dry ice. Frozen samples were normally sent once or twice a month in dry ice. For the time they are in the freezer, data loggers are required to ensure the correct storage temperature. When the sample is in the package and ready to go, I contact the courier and schedule the pick-up for that day.

REGISTRATION OF DATA IN THE PATENT FILE (PAPER OR ELECTRONIC)

During or after the visit, the doctor must register everything in the patient file. In CHVNG/E, I dealt with mostly paper files, and in HGO the files were all electronic. In clinical trials, "what is not written did not happened". The completeness of the visit records will reflect the quality of the visit procedures themselves, and will be the support for a well completed CRF.

Doctors are not prepared to register all the information required for clinical trials as their daily practice. To ensure this registry, in CHVNG/E we created checklists with all topics that must be written, and in HGO we were next to the doctors telling them what to write.
In the screening visit, it must be recorded the hour in which the patient signed the ICF, and what was the version. All inclusion and exclusion criteria must be checked, and that has to be written. It is important to collect and register the time blood was drawn, vital signs were measured, or the ECG was performed. If the patient must rest for 5 minutes before assessing his blood pressure, it must be registered that the patient rested for 5 minutes before the measurement. All concomitant medication taken by the patient from the moment of informed consent (or previously when required) must be registered, including start date, end date, dosing and therapeutic indication. To remember what to advice to the doctor to write, I try to think in the CRA's point of view: he can only know if we complied with the protocol if that it is written.

AEs and SAEs

In the screening visit, every condition the patient had must be assessed and recorded as baseline conditions. From that time forward, all new adverse events (AEs) or worsening of baseline conditions must be registered in the patient file and reported to the sponsor in the CRF. If the events meets the seriousness criteria, it is a Severe Adverse Event (SAE) and it must be reported in 24 hours, in the CRF or using the sponsor paper SAE form, depending with the protocol. When gathering information on AEs, it is important to collect start and end date, intensity, causal relationship with the IMP or study procedure, and outcome of the event. Intensity may be graded just as mild, moderate or severe, or it can be graded using the CTCAE grade (Common Terminology Criteria for Adverse Events). CTCAE has five levels, classified as following: grade 1 – mild; grade 2 – moderate; grade 3 – severe; grade 4 – life-threatening; grade 5 – dead.
It is very important to collect information on AEs and SAEs correctly, as it will be crucial to the benefit-risk analysis of the IMP.

Compliance verification

In every visit, patients must always bring all the medication they have in their possession. Counting the number of pills (or injections, etc.) is the only way to know whether the patient took the study drug or not. If more pills are returned that those expected, that means the patient missed doses. If he returns less pills that expected, he may have taken more than it was supposed to or he may have lost some pills. I always encourage patients to be compliant and to return all medication, although sometimes they forget it. The number of returned pills must be registered in the patient file, but the ultimate responsible for accountability is the pharmacy.

CRF COMPLETION

Every patient visit has a corresponding CRF page that must be fulfilled. CRFs may be in paper or electronic, although I only worked with electronic ones. There are several platforms used by sponsor, designed to collect the information required for the statistical analysis and retrieve the key information on the study. CRFs must be completed as soon as possible, as it is easier to remember data right after the visit.

CRFs are all similar, despite of the platform used. They ask for the visit date, measurements, results, timings, AEs and concomitant medication. The biggest difficulty in completing CRFs in CHVNG/E was due to the illegible handwriting of most physicians. It took a lot of time to decode, and some brainstorming with my colleagues occasionally. Electronic records are much easier in that aspect.

After data is introduced in the CRF, it will be reviewed by the CRA and by the study data managers. If they detect any discrepancy, they launch queries for the site to resolve. The best way to avoid queries is to ensure a good registration of data in the patient file. Although, there are always queries and their management takes some time and effort. Data managers do not understand want happens in the visits and are very strict to the protocol and not much open to daily hospital practices.

PATIENT REIMBURSEMENTS

Patients in clinical trials must not have expenses incurring from their participation. So, expenses related to transport to the hospital and food in the visit days are all reimbursed by the sponsor. In both hospitals, I must gather the receipts from the patients, check if the dates match the visit dates (or the days before, if it is a receipt from gas or public transportations) and register them all to keep tracking. Reimbursement can be done by various ways. The most common is to deliver the receipts to the CRA, which will bring the money in the next visit, although none of us likes to carry money, because there is always the risk of losing it. In HGO, the hospital has a system in which the patient fulfils a form with the annexed receipts, the hospital bills the sponsor, and then the money is transferred to the patient or he could get it from the hospitals treasury.

MAINTENANCE OF MATERIALS' STOCK

During the studies in which samples are sent to a central laboratory, collection kits and shipping documents and boxes are materials we must always have available in the site. In CHVNG/E we created excel tables to register every time a kit arrived, was used or destroyed, and the sheet automatically displays the number of kits available. As expiration dates approached, we configured

email alerts to remind us to destroy the kits and avoid they are used expired. This worked very well. Although, in HGO there was no table for controlling kits. They are all in a cabinet where we can see them, and we can know how many kits are available, but this system is less rigorous than the control performed in CHVNG/E. When we realise the material are running low and order more, sometimes they do not arrive in time. In these situations "repeat" and "unscheduled" kits must be used, choosing the appropriate tubes for each visit according to the lab manual. In the beginning, these issues bothered me a little bit because in CHVNG/E there was a great control of stocks. The truth is I became more prompt to solve problems after dealing with this situation. I created one excel table similar to the ones used in CHVNG/E for the HGO's pneumology service. Although, it is in Cardiology that more samples are sent and more materials spent: the volume is so high that it is a table is not a practical method of control. My suggestion was to define a specific day in the week to verify materials and order more as necessary, ensuring these situations are minimised.

3.1.8. STUDY CLOSE-OUT

After all patients finished the study, the sponsor will eventually perform its close-out. I assisted two close-out visits, where the CRA comes to the site and verifies all documents, ensuring the dossiers can be closed and remain archived during 15 years. As they cannot be moved, and they can be subject of audits and inspections, all documents must in place and compliant with applicable laws.
In a close-out visit, we must provide the CRA the investigator site file, patient files, and all source documents from clinical visits and from the pharmacy logs. In this visit, the CRA would collect all unused materials form the site, such as kits, ECG machines, computers and data loggers.
All trial dossiers are marked as closed, and should be archived according to the conditions stated in ICH-GCP.

3.1.9. MONITORING

Each clinical trial has a monitor or CRA, which is the responsible person from the sponsor or CRO to ensure that we, in the site, are complying with the protocol, ICH-GCP and safeguarding the rights of subjects. For this, CRAs perform Source Data Verification (SDV): in each monitoring visit, they compare the data in source documents to the data registered in the CRF.
To prepare a monitoring visit, I must ensure that all CRFs are up-to-date, the queries I could resolve were addressed, and the patient files and ISFs are organised and up-to-date. When the CRA comes, I must provide him with all the documents so he can do SDV, and I and the PI must be available to resolve any identified issues and explain eventual situations.
CRAs often are a great help for the site staff, even out of monitoring visits. They are almost always available by phone and prompt to help us and answer our last-minute questions.

3.2. ACTIVITIES RELATED TO CLINICAL RESEARCH OFFICE IMPLEMENTATION AND INTEGRATION WITH BLUECLINICAL

The state of integration of Blueclinical and the office in the hospital structure was completely distinct from one hospital to another. In CHVNG/E, GAGIC was fully integrated in the hospital structure, although there were still some administrative constraints. A few days after beginning the internship, I had a mechanographic number, access to the hospital's Wi-Fi network, and a set of two white coats. When addressing a person from the hospital I never met before, I would say "Hello, my name is Daniela and I am from GIC" and most persons in the hospital would recognise GIC as an entity. In HGO, only a small number of doctors know there is a company named Blueclinical who has a partnership with the hospital. CIC is not recognised by anyone. When addressing someone new, or that person would knew my colleague and I would say I work with her, or I would have to explain the history from the beginning. After two months in the hospital, I still not have a mechanographic number. I wear a white coat, but because the staff in the clothing department facilitated the process.

After this brief context, I state below some activities I performed not related to a specific clinical trial.

3.2.1. HISTORICAL DATABASE OF STUDIES AND PAYMENTS

One of the first tasks I did in CHVNG/E was to elaborate the history of clinical trials and observational studies that occurred after 2008. There was one table to register general information about each trial in that period, and that was another one that I created to collect payments data. The purpose was to establish a "baseline condition" to allow comparisons between before and after the partnership. Data was very disperse through the hospital and it was not easy to gather. Most of the data we could retrieve from the financial department, which had saved some information about the studies involving payments. In the pharmaceutical services there was also a control table, but only about clinical trials requiring medication (there was no data on observational studies). Some other information was in the hospital's annual report. The rest of the information we retrieved from the lost dossiers and papers in the clinical services. In the end we had created an excel table compiling all sources and that is presumably complete.

Besides that database I created an excel document to control payments only. Even if the partnership increases the number of trials, that is no guarantee of an increase in the income and so we need to control that too. Again, some information I got from the financial department, but it was not very correct as the same trial may have different names in different documents, and it was a little bit

confusing. Some clinical departments had tables of their own. Most data I got from listing sponsor names from the studies database and questioning each one about which payments happened after 2008. That is time consuming for us and for sponsors, and so when I left CHVNG/E this payment history was still incomplete.
In HGO there was already a historical database, although not very complete, which was created by the existing structure to support research.

3.2.2. Presentations to the Clinical Services of The Hospital

In CHVNG/E, the partnership with Blueclinical and the recently formed GIC were presented to the departments in a formal meeting that occurred in July 10th. This presentation was essential to the divulgation of Blueclinical, to let the doctors know who we are and how can help them. As the partnership is between one public and one private entity (and these are not well-seen in the Portugal's present) it is also necessary to break some myths and to clarify what both parts are winning with this.
The GIC strategy at the time was to perform, beyond this one, a presentation to each clinical department (where more doctors could attend and the discussion could be more personalised). We decided with GIC's coordinator to start supporting the services only after the office had been individually presented to the service, from doctor to doctor. The true is that the doctor to doctor approach works better, although they all have very complicated agendas and it was very hard to conceal everyone's availability to schedule some of the meetings. When I left CHVNG/E, in the end of February, GIC was still lacking presentation to a few departments.
My experience told me that these individual meetings are not feasible. We ended up helping departments before they met us formally, and there were trials in which we could have entered a lot earlier if it was not for this. Although, I understand their importance and I would suggest to try to condense two or three departments at each time; or to open the initial formal meeting to all the hospital community.
During these meetings, doctors always seem more interested in their small and casuistic studies than in clinical trials. Many of them never performed trials, and so they are more interested in statistical support and medical writing.

3.2.3. Questionnaire of Interests

The questionnaire of interests is a major tool in the development of Blueclinical CRP: It is an electronic questionnaire that must be sent to every doctor in the network, which contains basically a list of therapeutic indications. Doctors must choose those indications they would like to investigate. With that information, Blueclinical would be able to characterise the interests of Portuguese

doctors and attract to the hospitals clinical trials of their interest. What happens now is that Portugal must conform with the trials the sponsors decide to bring to Portugal (which are normally those harder to recruit, or those which are too complicated and do not succeed in other countries).
In CHVNG/E, the link to the questionnaire was initially sent by emails using institutional mailing lists. It did not succeed because most doctors do not use that email. The next strategy was to print questionnaires and, using a list of all doctors as control, going personally to each doctor to get the answers.
In HGO the link was also sent by email, first to the institutional emails of physicians, and then to their personal ones. After a few complication, we now have also a control list with all the names per department. There is less time available to perform these tasks as the volume of clinical trial visits is higher. Although, despite the few responses gathered, the questionnaires already led to a success case: there was one new trial for venous thromboembolism proposed to the cardiology department; from the database of responses we saw that two internists were interested in that area, and now the team is composed by both departments.

3.2.4. WEBSITE

One objective of CRP is to have information about each office in the hospital's internal and external website. As there is no template available yet, every CRC gave his contribute to the construction of the contents. In CHVNG/E, the information is already available in the internal website.
Generally, the information covers: important news and information; GIC organisation and contacts; SQIC; frequent asked questions (by patients, physicians and sponsors); and a list ongoing of clinical trials. What is displayed in the internal and external website depends on the applicability: contents directed to patients or sponsor must be available in the external platform, as contents which are specific for doctors may be only available in the internal platform.
I believe that having a website is a useful asset, as the partnerships are new and not very widespread, both inside and outside the hospital's facilities.

3.2.5. RESOLUTION OF ADMINISTRATIVE CONSTRAINTS

The implementation of a new office in a hospital is a difficult task. Hospitals are rigid structures, and trying to change their methods will cause some constraints. That happened when trying to implement fee exemptions for trial patients, finding a way to reimburse patient expenses through the hospital, and trying to remove duplication of ethical approvals.
Participants in clinical trials must not have any expenses incurring from the trial; that includes user fees in consultations and examinations. In most hospitals they tell us there is no way to exempt the

subjects of the payment of those fees (that happened in CHVNG/E). In HGO there is an administrative code that was created to allow that exemption. I tried to understand how that code was created, as exemption is a legal requirement and must be implemented in all hospitals of the network. From what I understood, the clinical director of the hospital must authorise the creation of the code by the department of informatics, and then the exemption code is created in the same way as other legal exemptions (e.g. blood donors, oncology patients, low income subjects).

Relating reimbursement of patient expenses, the most common method is to deliver the receipts and receive the money through the CRA, having both of us to carry money. As this is somewhat risky, the ideal procedure would be the hospital to bill the value of the expenses directly to the sponsor. Then, the sponsor would pay the hospital, which will in its turn deliver the value to the patient, in physical money or by bank transfer. This method is possible in HGO, although they require a lot of data from the patients, such as bank account and several other numbers.

Other issue that could be avoided is the duplication of ethical assessments. Clinical trials must always be approved by the national ethics committee (CEIC). Clinical studies follow the same procedure after the law 21/2014 became effective, but previously they must only be approved by local ethics committees just as observational studies. The logical situation would be to never duplicate assessments, and only studies not undergoing CEICs revision must be submitted to local ethics committees. In CHVNG/E we were able to eliminate this duplication, but in HGO it still exists and it is one big constraint hindering approval times.

3.3. ADDITIONAL TRAINING

During the whole internship I performed several trainings in e-learning platforms and also face-to-face training provided by the company.

The first training was only one week after the internship interview, when I had not yet started the internship itself. In that training I was taught a lot the Blueclinical project and ambitions, and specifically about quality management, effective communication, and values and standards.

During the first days in CHVNG/E, I needed to complete several e-learning trainings about ICH-GCP, informed consent process, InForm (a CRF platform), fraud and misconduct, AEs and SAEs and sample shipping. I was already familiarised with some of the concepts from my academic background, but nevertheless they were useful to remind some ideas and to have a proof of training as they provide certifications.

During the course of the internship, I attended several training sessions provided by Blueclinical. Many of them were presented by the colleague working directly with that specific subject, what was a very enriching experience because I felt more motivated to ask questions and collaborate

with the discussion. These trainings covered applicable laws and regulations to clinical trials and medical devices, specific day-to-day subjects of a CRC life such as recruitment practices, ICF, screening and randomisation, overviews of procedures from feasibility to close-out. I also got insights on data management and the processing of human biological samples in clinical trials.
Everything is recorded in a training log, whose template is provided by Blueclinical.
Apart from general training, each clinical trial protocol requires the completion of a set of trainings in order to become a member of the study team and to receive credentials for study platforms.

4. DISCUSSION

Having the opportunity to contact with two different hospitals was a very enriching experience. When I initially faced the change of hospitals I was not so excited to leave the team I knew and my comfort zone, but I now see it as a positive change: I feel more independent, I learned a lot about patient visits and other procedures, and I now have a comparative insight otherwise I would have not. Overall, the change made me grow, professionally.

In the beginning of this internship I was very insecure of my own. For example, I would ask for someone to review my emails before sending them all the time and I was afraid of answering phone calls. Slowly, with encouragement and by gaining experience, I became more autonomous and more confident of myself, and I started taking responsibilities of my own.

In CHVNG/E there were four CRCs, myself included, and we had a very supportive working environment. The work was divided between the four of us, and at the end of most days I felt like I could achieve my objectives for the day. I helped directly in a few patient visits, but most of the time I dealt with submissions and administrative tasks. We divided the trials between ourselves, irrespective of their status, and so I ended up learning more about submission processes than patient visits.

The background from the previous year of the master's course provided me a solid knowledge about the contents I faced in the internship later on. Although in the beginning I did not know exactly what the functions of a CRC were, I realised after some time that I actually knew how to get things done in theory. After some time living the practice, it was quicker to learn about the roles I was supposed to perform. The medical contents I learned in the BSc in Biomedical Sciences were also useful, as I could have a better understanding of the mechanisms of disease implied in clinical trial protocols. Without any doubt, I was able to understand what it is to be a clinical research coordinator during the internship, which was my main goal.

Despite how much I learnt with this internship, there was some subjects I have never dealt with. I never performed submissions or helped directly with clinical studies of medical devices. I never had any audit or inspection during this time frame also. I believe being involved in a quality audit or inspection is a big lesson for someone working daily with the procedures being verified.

There were several procedures that I found to be less efficient during the internship, most of them I already focused in the previous sections. The main one is related to the analysis of financial protocols in submission phases. I feel like I needed to perform a task I was not sure how to perform, and I ended up taking a lot of time doing it that had no revenue. Happily that is already

solved, as there is one person in the company responsible for negotiating contracts for the entire network.
Other aspect I did not felt so comfortable about was the request for archiving fee to the sponsors. Presently that is not done, but in the beginning it caused me some constraints. Initially I was though to request the sponsors to directly contract an archiving company. Some sponsors could accept this, but one of them who could not suggested us to request an archiving fee, which was higher than the effective cost of the archiving company. I agree with the procedure of requesting a fee and I understand that we need to evolve with experience, as a company. What I disliked was to lack a justification for the amount I was requesting, which let me uncomfortable. Besides, I dealt with one sponsor that had a trial in submission during this transition process and to which I had to justify successive changes in the procedures.

Looking back at the internship, there are still a lot of aspects I need to improve if I aim to become a better CRC. I became more able to communicate naturally instead of getting nervous anytime, although I believe I could improve even more by using negotiation techniques and by expressing my point of view more clearly in every conversation. My time management skills were improved, mainly in HGO where time is a very scarce resource, and by having to conciliate the internship activities with the writing of this report. Although I feel that I leave the hospital in the end of the day with things left to be done frequently, and that indicates that time management still requires improvement.
Overall, I made a lot of mistakes during my internship, and I must thank my colleagues in both hospitals for helping me overcome them. Facing mistakes can be demotivating sometimes, but my colleagues always told me the errors are a sign I am trying and everybody commits them. I learned a lot from my own errors: I became more oriented to solutions instead of self-punishment; and I could analyse my actions in order to identify the mistake not to repeat it.
From the ground knowledge I gained, I now feel like I have the opportunity to grow on my own and to learn and accomplish more in my professional life.

In general terms, I believe the initial goals were achieved. The main goal of understanding the role of a CRC was fully accomplished, and the secondary goals were also fulfilled although I should still work to improve them daily.

5. CONCLUSION

This internship in Blueclinical was my first ever professional experience. I feel very grateful for having this opportunity of finishing and academic training already with a solid working experience. Clinical research coordination is a very wide activity that provides a good training basis to work as a CRC in the future, but also provided me with insights on other functions related to clinical trials.

I believe that my theory background from the Master's degree was a huge support to the activity I developed, as contents are very directed to daily practice approaches. The BSc degree was also helpful mostly for the soft skills I acquired.

I also feel grateful for the opportunity of learning in the middle of such an innovative, young company.

Actually, I am taking a professional internship for a year, also in Blueclinical, and I continue in HGO with the same functions as during the previous internship.

6. BIBLIOGRAPHY

1. Blueclinical. Quality Manual. 2014.

2. Soares N. Inovação em contraciclo. Nortemédico [Internet]. 2013; Available from: https://www.blueclinical.com/pt/artigo.php?type=1&id=1

3. Blueclinical. Consultadoria de I&D.

4. Blueclinical. Blueclinical Phase I.

5. Blueclinical, CHVNG/E. Protocolo de Colaboração entre o Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E. e a Blueclinical - Investigação e Desenvolvimento em Saude, Lda. 2013.

6. CHVNG/E. Centro Hospitalar de Vila Nova de Gaia/Espinho [Internet]. 2014 [cited 2014 Jan 5]. Available from: http://www.chvng.pt/

7. Orta HG de. Hospital Garcia de Orta [Internet]. [cited 2014 May 30]. Available from: http://www.hgo.pt/

8. National Institutes of Health (NIH). Guidance for Clinical Researchers [Internet]. Available from: http://www.nichd.nih.gov/health/clinicalresearch/clinical-researchers/Pages/index.aspx

9. ICH. ICH Topic E6 (R1) Guideline for Good Clinical Practice. 2002.

10. International Conference on Harmonisation. ICH Guideline E9 - Statistical Principles for Clinical Trials. 1998.

11. International Conference on Harmonisation. ICH Guideline E8 - General Considerations for Clinical Trials. 1997.

12. Almeida L. Overview of the R&D, approval and safety monitoring processes. Introduction to the product R&D process. 2012.

13. Pereira M. Principles of epidemiology. Design and conduct of epidemiological studies. 2013.

14. Carlson MDA, Morrison RS. Study Design, Precision, and Validity in Observational Studies. J Palliat Med. 2009;12(1):77–82.

15. Apifarma. Ensaios Clínicos em Portugal. 2013.

16. Chin R, Lee BY. Principles and Practice of Clinical Trial Medicine. 2008.

17. World Medical Association. World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013.

18. Edwards LD, Fletcher AJ, Fox AW, Stonier PD. Principles and Practice of Pharmaceutical Medicine. 2nd ed. John Wily & Sons, Ltd.; 2007.

19. ICH. The Value and Benefits of ICH to Industry [Internet]. 2000. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Vision/Value_Benefits_for_Industry_2000.pdf

20. European Medicines Agency. European Medicines Agency [Internet]. [cited 2014 May 24]. Available from: http://www.ema.europa.eu/

21. European Comission. Medicinal Products for Human Use [Internet]. Clinical Trials. [cited 2014 May 24]. Available from: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

22. European Comission. COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or im [Internet]. 2005. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

23. Assembleia da República. Lei n.º 46/2004, de 19 de Agosto. 2004;

24. European Comission. 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.

25. Fabio A. Thiers, Anthony J. Sinskey ERB. Trends in the globalization of clinical trials. Nat Rev Drug Discov. 2008;7:13–4.

26. ClinicalTrials.gov. Studies on Map [Internet]. [cited 2014 May 13]. Available from: http://clinicaltrials.gov/ct2/search/map/click?map.x=720&map.y=232

27. EvaluatePharma. World Preview 2016. 2010.

28. PriceWaterHouseCoopers. Pharma 2020: The vision. Which path will you take? 2007.

29. Silveste S. Introduction to Drug Discovery. Relevant approaches in drug discovery, design and development. 2012.

30. European Medicines Agency. Non-clinical Assessment Requirements. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/06/WC500107868.pdf

31. Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie CCP, Bernard H. Munos SRL and ALS. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–14.

32. Infarmed. Estatisticas de Avaliação de Ensaios Clínicos pelo Infarmed. Gráficos 2006-2013.

33. Blueclinical. Orientação Estratégica. 2013.

34. Ministro defende nova lei para ensaios clínicos. Diário de Noticias. 2013;