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Ema Sofia Lisboa Órfão

Relatório de Estágio Curricular na Blueclinical Lda.

Curricular Training Report in 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 relatório aos meus pais.

o júri

Presidente	Professor Doutor Bruno Miguel Alves Fernandes do Gago professor auxiliar convidado da Universidade de Aveiro
Arguente	Professora Doutora Maria Joana da Costa Gomes da Silva professora adjunta da Universidade de Aveiro
Orientadora	Doutora Cristina Manuela Pinto Vieira Lopes diretora de operações clínicas e desenvolvimento de negócio da Blueclinical Lda.
Orientadora	Professora Doutora Alexandra Isabel Cardador de Queirós professora coordenadora sem agregação da Universidade de Aveiro

agradecimentos

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palavras-chave

Estudo clínico, dispositivos médicos, unidade de fase I, *site management organisation*, *clinical study coordinator.*

resumo

O presente relatório descreve com detalhe o meu período de estágio curricular como gestora de projeto. O estágio teve a duração de 9 meses e ocorreu na Blueclinical Lda, uma empresa constituída por três unidades de negócio distintas: uma unidade de fase I, serviços de gestão e coordenação de centros de ensaios e serviços de consultoria farmacêutica.

A principal atividade desenvolvida foi a gestão de um estudo clínico com um dispositivo médico implantável ativo. Durante o período de estágio pude também desenvolver outras tarefas ao longo dos diferentes setores e compreender o seu funcionamento.
Para além da descrição das atividades desenvolvidas é feita uma apresentação das principais dificuldades sentidas, das estratégias utilizadas para as ultrapassar e dos objetivos que acredito ter alcançado.

Este estágio constitui o meu primeiro contacto com o mundo do trabalho, tendo-me permitido aplicar e aprofundar os conhecimentos e competências adquiridos ao longo do meu percurso académico, concretamente durante o primeiro ano do Mestrado em Biomedicina Farmacêutica.

keywords

Clinical study, medical devices, phase I unit, site management organisation, clinical study coordinator.

abstract

The present report describes in detail the period of my curricular training as a project manager. The training lasted 9 months and occurred in Blueclinical Ltd, a company composed of three distinct business units: a phase I unit, site management organisation's services and pharmaceutical consulting services.

The main activity developed was the management of a clinical study of an active implanted medical device. During the training period I could also perform other tasks over the different sectors and understand its operation.
Along with the description of the activites perform, it is done a presentation of the main difficulties encountered, the strategies used to overcome them and the goals that I believe I have achieved.

This training constituted my first contact with the world of work, and allowed me to put into practice and deepen the knowledge and skills acquired throughout my academic course, particularly during the first year of the Master in Pharmaceutical Biomedicine.

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LIST OF ABBREVIATIONS

AB	Administration Board
AIMD	Active Implantable Medical Device
AUC	Area Under the Curve
BA	Bioavailability
BE	Bioequivalence
C_{max}	Maximum Concentration
CIP	Clinical Investigation Plan
CEIC	Comissão Ética para a Investigação Clínica
CES	Comissão de Ética para a Saúde
CNPD	Comissão Nacional de Proteção de Dados
CRA	Clinical Research Associate
CRF	Case Report Form
CSA	Clinical Site Agreement
CSC	Clinical Study Coordinator
CTA	Clinical Trial Application
CV	Curriculum Vitæ
EC	European Comission
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INFARMED	Instituto Nacional da Farmácia e do Medicamento
ISO	International Organisation for Standardisation

LTD	Limited
MD	Medical Device
MS	Member State
MSA	Master Study Agreement
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
R&D	Research and development
SMO	Site Management Organisation
SOP	Standard Operation Procedure
$T_{1/2}$	Half-life Time
T_{max}	Time to reach maximum concentration
TMF	Trial Master File
QREN	Quadro de Referência Estratégico Nacional

1. INTRODUCTION

The present report describes my training experience at Blueclinical Ltd, which constitutes part of my Master's degree in Pharmaceutical Biomedicine. The internship lasted 9 months and started on 1st September, 2012.

At the beginning of my training, and taking in to account the characteristics of the host company, I defined a set of primary objectives:

- Develop a deep understanding about the regulatory framework of clinical trials and clinical studies;
- Perform regulatory submission to the different national entities in the context of clinical investigation studies;
- Develop and contact with different project management tools and techniques;
- Understand the functioning of a phase I unit;
- Understand basic concepts regarding the function and construction of a quality management system (QMS);
- Contact with the reality of a national research site;

I have also established a set of secondary objectives:

- To develop interpersonal and soft skills, i.e. communication (oral and written), self-confidence, critical thinking, organisation, problem solving, responsibility sense and autonomy;
- Establish a working contact network;
- Identify potential areas of interest within the pharmaceutical industry.

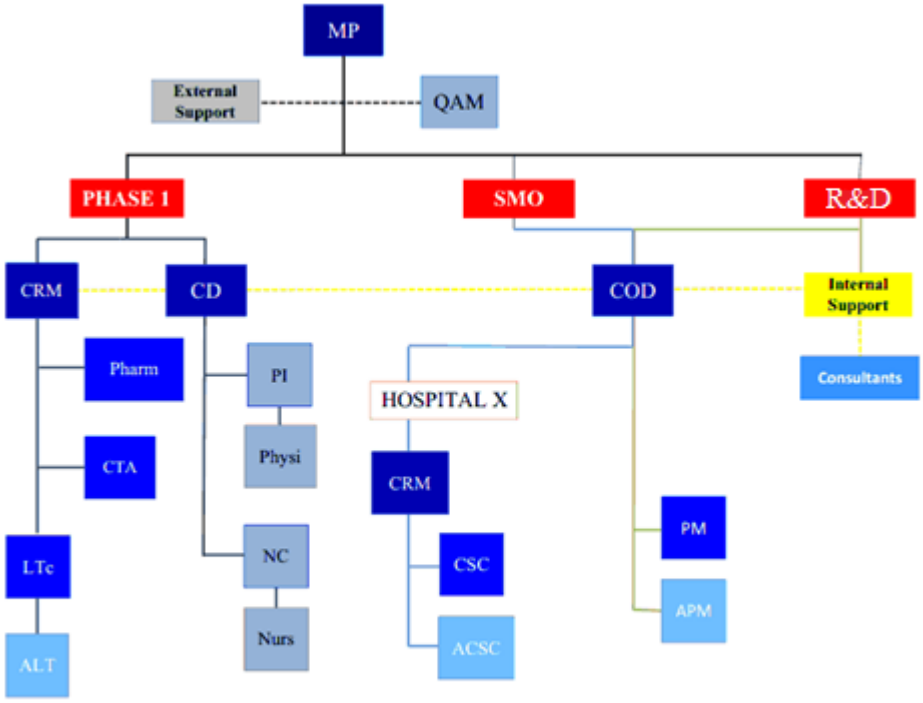
Regarding the report's structure and contents, this work is organised in five chapters. The first chapter includes, apart from the defined training objectives, an overview of Blueclinical's structure, mission and services. Chapter 2 gives respect to the state-of-the-art and here I present a brief description regarding the R&D model for medical devices (MD) and pharmaceuticals, highlighting some of their differences, as well as the applicable European regulatory framework concerning the clinical investigation process and the national situation. Chapter 3 entails a description of the activities developed and the different training sessions and meetings attendend. Chapter 4 corresponds to the discussion, where I describe in general terms the main difficulties felt and the learning outcomes achieved. The last chapter corresponds to the conclusion.

1.1. HOST COMPANY OVERVIEW

Blueclinical – Investigação e Desenvolvimento em Saúde, Ltd. is a company that was created in May 2012 and whose headquarters are located at Hospital da Prelada, level 3 – Ala Poente, Rua de Sarmento de Beires, 153, 4250-449 Porto.

According to the type of services provided, Blueclinical is formed by three business units: Blueclinical SMO, Blueclinical Phase I and Blueclinical R&D (figure 1). These three business units allow Blueclinical to provide a complete range of services and competencies that cover all the different phases of the drug discovery process – *from bench to bedside*.

Figure 1 – Blueclinical's general structure.



ACSC: Associate clinical study coordinator; **ALT:** Associate laboratory technician; **APM:** Associate project manager; **CD:** Clinical director; **COD:** Clinical operations director; **CRM**: Clinical research manager; **CSC:** Clinical study coordinator; **CTA:** Clinical trial assistant; **External support**: Human resources, accountability, purchasing, finances; **Internal support:** Medical writing, statistics, pharmacokinetics, pharmacovigilance; **LTc**: Laboratory technician coordinator; **MP:** Managing partner; **NC:** Nurse coordinator; **Nurs:** Research nurses; **Pharm:** Research Pharmacist; **Physi** - Research physicians; **PI:** Principal investigator; **PM:** Project manager; **QAM**: Quality Management; **R&D:** Research and development; **SMO**: Site management organization.

SMO states for 'site management organisation', and in general terms it consists in organisations specialised in managing clinical research sites. Therefore, Blueclinical SMO intends

to operate by establishing partnerships with target national hospitals, enhancing their ability to carry out research of excellence through its operational management; this is accomplished by integrating clinical study coordinator (CSC) onto the clinical research sites (1).

The ultimate goal is to develop a network of highly effective clinical research sites.

Blueclinical Phase I consists in a Human Pharmacology Unit located in Hospital da Prelada, Porto. Blueclinical has also established a protocol with Hospital CUF Descobertas, Porto.

Blueclinical Phase I mission is the conduction of Phase I clinical trials, in healthy volunteers (at Hospital da Prelada) and in selected populations of patients (at Hospital CUF Descobertas). Its creation was based on the purpose of generating new opportunities at the clinical research level, mainly in the early stages of the clinical development, and as a way of supporting other companies in the development of their programs (2).

The clinical team is composed by the clinical director, a group of medical investigators and their coordinator - the principal investigator (PI), and also a team of nurses and their coordinator. The phase I team also includes laboratory technicians, one pharmacist and the clinical research manager.

Blueclinical R&D is focused on providing consulting services in pharmaceutical, non-clinical, clinical, regulatory and commercial development. The target client goes from national and international start-ups to universities and other public or private institutions. Blueclinical R&D services include:

- Development of the global R&D plan of new drugs, MDs, and other health products;
- Preparation and monitoring of the scientific and regulatory advice processes for regulatory authorities;
- Planning and supervision of pharmaceutical development and analytical methods;
- Defining and monitoring of the implementation of the nonclinical development plan;
- Preparation of the investigator's brochure and investigational medicinal product (IMP) dossier;
- Definition and monitoring of the clinical development plan;
- Ethics and regulatory approval of clinical studies/trials;
- Support in portfolio selection;
- Business plan analysis;
- Development of business plans and applications for obtaining financial support (3).

Blueclinical R&D has also a group of external consultants experts in their area of action,that collaborate with the company.

2. STATE-OF-THE-ART

The pharmaceutical and the MD industries constitute two major players in human health (4).

Pharmaceuticals are molecular-based compounds whose effectiveness depends on its interaction with the subject's physiologic system (5). MD are generally engineer-based products with localised effects and whose good performance is dependent on their correct use. Given this obvious divergences, the two development models are also significantly different and, consequently, subject to different regulatory frameworks (4).

2.1. R&D MODEL FOR PHARMACEUTICAL PRODUCTS

The drug discovery process begins with developing a deep understanding of the disease and their causes. After this, scientists start looking for a "target", i.e. a gene or a protein, and try to demonstrate that it has a role in the disease's physiopathology. This "target validation" is done through the conduction of a series of experiments in living cells and animal models of disease. The next step is to find/develop a series of molecules/ "lead compounds" capable to interact with the selected target and cause the desired effect (6).

These molecules are then subject to a series of tests (e.g. pharmacokinetic (PK) and toxicology tests) whose results will determine which compounds present the necessary characteristics to continue. After this initial screening, the remaining molecules' structures are optimised in order to improve their properties (6).

Before entering in clinical development, the compounds that arrived to this stage are tested in vitro and in vivo (animal studies) – the non-clinical development. The information obtained is used to estimate a safe starting dose and doses range for clinical trials (7).

In order to bring the new drug to the market a sponsor has to prove its efficacy, safety and quality through a series of clinical trials.

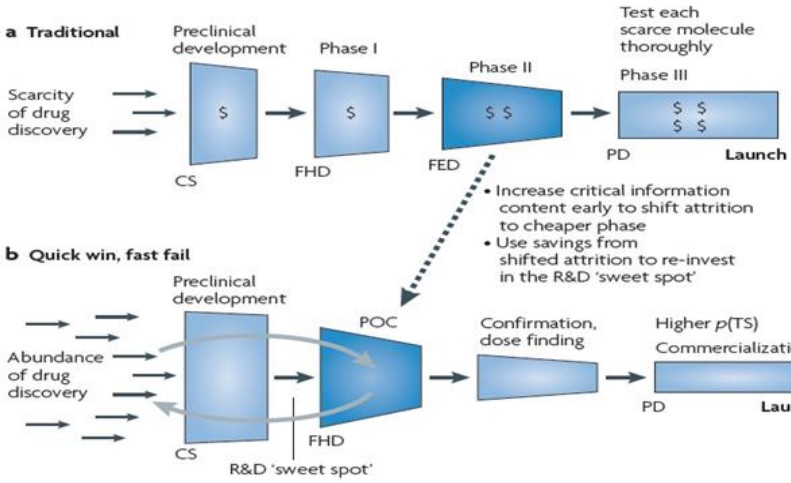
Traditionally, clinical trials have been divided in four phases:

- Phase I - studies designed to estimate tolerability and characterise the PK and pharmacologic profile of the IMP (7);
- Phase II – studies whose primary objective is to explore the therapeutic efficiency of the drug candidate in patients; generally this is sub-divided in: phase IIa trials, that often use dose escalation designs for estimating the dose response, and phase IIb trials, that evaluate the efficacy of the drug candidate at the prescribed dose regimen (8, 9);

- Phase III – studies design to confirm that the drug is effective for use in the intended indication and population. The data generated will support the "prescribing information";
- Phase IV – studies conducted while the drug is already on the market (8);

Data shows that nowadays the clinical development process has an average duration of nine years and constitute 58,6% of the product development costs. Also, the traditional and sequential model for drug development has been accused of being slow, expensive and shortly predictive of the true clinical effectiveness of the study drug (10). Several cases of big failures during the late stages of the clinical development process have led to the creation of a new development model: the "quick-win, fast fail" paradigm (figure 2) (11).

Figure 2 – The traditional paradigm vs. the "quick win, fast fail" paradigm. Available from: Paul, Steven M. , 2010 (11).



CS: Candidate selection;
FED: First efficacy dose;
FHD: First human dose;
PD: Product decision;
POC: Proof of concept;
***p*(TS):** Probability of success.

This new approach intends to reduce technical uncertainty in the early stages (phase I/IIa) through the use of new tools and strategies. A good example is the conduction of proof-of-concept trials that will have the capacity of providing evidence that the molecular target is being hit and causing the desired physiological response (11, 12).This will result in a small number of new molecular entities entering in phase II/III but those that advance have a much higher probability of success. The savings gained from preventing costly failures can then be re-invested to further enhance R&D productivity (11).

The process of granting a marketing authorisation for a certain medicine is based on risk/benefit analysis of the data produced during development. The assessment is done by the

European Medicine Agency – centralised procedure, or by the different national competent authorities of the countries in cause - national, mutual recognition or decentralised procedures (13).

2.1.1. CLINICAL TRIALS – REGULATORY FRAMEWORK

Clinical research is an extremely regulated sector, with a series of laws and ethical standards in place. Their main purposes are to protect the rights and integrity of patients and study volunteers and to guarantee a high quality of the data produced/collected.

The requirements for the conduction of clinical trials in Europe are established in the following documents:

- Declaration of Helsinki;
- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP);
- Directive 2001/20/EC, April 4th, on the approximation of the laws, regulations and administrative provisions of the Member States (MS) relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use;
- Directive 2003/94/EC, October 8th, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and IMPs for human use;
- Directive 2005/28/EC, April 08th, laying down principles and detailed guidelines for GCP as regards IMP for human use, as well as the requirements for authorisation of the manufacturing or importation of such products;
- Directive 95/46/EC, October 24th, on the protection of individuals with regard to the processing of personal data and on the free movement of such data (14).

The clinical trials' directive 2001/20/EC has been in place since May 2004 and represents the first attempt of the MS to harmonise the clinical trial approval process.

According to this directive, the conduction of a clinical trial is subject to a prior approval from two entities: the national competent authority and the central ethics committee of the country in question(15). In the context of a multicountry trial this results in multiple submission of the same documents to the different entities cross-country (15).

Despite some improvements, the clinical trial directive 2001/20/EC did not provide the required level of harmonisation and it corresponds to the most criticised part of all the European medicines legislation (15, 16).

In fact, data showed that the directive had led to a significant delay in the approval of clinical trials, an increase in the costs involved and in a 25% reduction on the number of clinical trial applications (CTA) between 2007 and 2011 (16).

As a consequence the European Commission has classified the need for new legislation as a priority in order to re-establish Europe's competitiveness in terms of clinical research and on 17 July 2012 a legal proposal for Clinical Trial Regulation has been adopted (16).

The proposal intends to facilitate the conduction of multicenter trials by creating a new and simplified authorisation procedure. In short terms, this procedure will involve the construction of a submission dossier with two different parts: the "general part", which will contain scientific information identical for all the MS, and the "national part", that will include ethical and local information (e.g. compensation arrangements, insurance, and informed consent forms). The dossier submission will be done through a portal – the "EU portal" (15, 16). The sponsor will be responsible for selecting a MS that will act as the "reporting MS" and will evaluate the "general part" of the submission dossier and prepare a report. The "national part" is evaluated by each MS. The two evaluations are followed by a pre-defined period during which questions can be raised (15).

As this proposal will assume the form of a regulation (instead of a directive) the harmonisation of the rules governing the conduction of clinical trials in Europe will be safeguarded from different transpositions by the several MS (15).

In terms of scope, the proposal covers all the interventional clinical trials of medicines for human use. Trials that involve no intervention are excluded. Moreover, it establishes that the so called "low-intervention clinical trials" (e.g. trials where the study drug is marketed and used in accordance with the terms of its marketing authorisation) should be subject to shorter timelines for approval (16).

Projections state the regulation is expected to be effective in 2016, followed by a 3-year period during which both the directive 2001/20/EC and the regulation will be in place (15).

2.1.2. CLINICAL TRIALS IN PORTUGAL

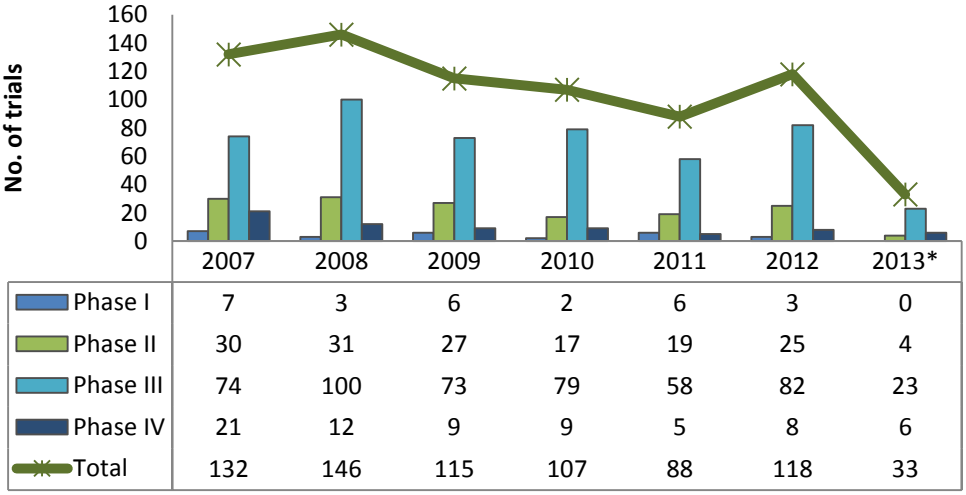
The national framework for clinical trials is mainly governed by laws transposed from European Directives, namely Law nr. 46/2004, August 19th, which is the transposition of European Directive 2001/20/EC. According to it, the sponsor has to get approval / favourable opinion from the following entities:

- National regulatory agency – Instituto Nacional da Farmácia e do Medicamento (INFARMED);

- National central ethics committee – Comissão de Ética para a Investigação Clínica (CEIC);
- National data protection committee – Comissão Nacional de Proteção de Dados (CNPD);
- Administration boards (AB) of all the sites involved.

According to INFARMED statistics, the number of CTAs in Portugal has also faced a decreasing period. Furthermore, there is a clear reduction in the number of early stage studies, being the majority phase III trials (figure 3) (17).

Figure 3 – Number of clinical trials submitted to INFARMED between 2007 and 2013, by trial phase. Adapted from: INFARMED's Website(17).



	2007	2008	2009	2010	2011	2012	2013*
Phase I	7	3	6	2	6	3	0
Phase II	30	31	27	17	19	25	4
Phase III	74	100	73	79	58	82	23
Phase IV	21	12	9	9	5	8	6
Total	132	146	115	107	88	118	33

*The 2013 data corresponds only to the 1st trimester.

When analysing the principal hurdles for conducting clinical investigation in Portugal it is important to mention the difficulty in implementing the trial at the site level (start-up phase). In this context, two factors are worth mentioning:

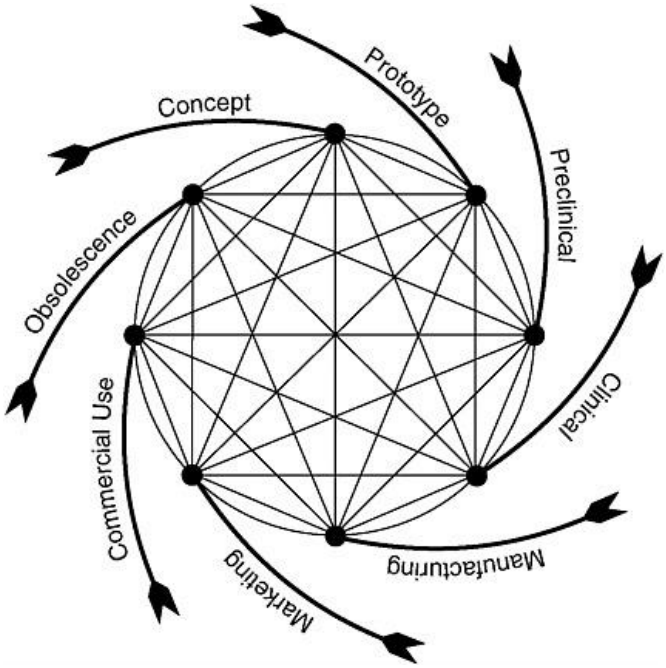
- Although CEIC is the legal organism for the ethical evaluation of clinical trials, the reality is that several national sites do not approve a trial without a favourable opinion of their local ethics committee – Comissão de Ética para a Saúde (CES). This unnecessary "double" ethical approval might significantly delay the overall approval process.
- Prior to the initiation of the clinical trial, the sponsor and the trial site must enter into a financial agreement. The negotiation process is generally time consuming, mainly due to the absence of a financial agreement standardised template.

2.2. MEDICAL DEVICE'S R&D MODEL

According to EUCOMED, the European MD industry as estimated market site of € 100 billion and employs more than 575,000 persons (18). Compared with medicines, the MD definition encloses a completely different range of products, from a simple pair of medical gloves to complex magnetic resonance devices (5). Taking this into account, the process of device development can also follow different paths.

Nowadays the majority of new and innovative devices have origin in small start-up companies (19) and in contrast with what happens for new drugs, the process of developing a MD doesn't start with a scientific discovery per se (5), instead the idea normally comes from a physician/engineer that conceives an idea for an unmet need and then constructs a prototype (figure 4) (19).

Figure 4 – The MD development pathway. Available from: Rare diseases and orphan drugs: accelerating research and development, 2011(5).



Generally it is possible to test several devices' properties in an engineering setting before moving to non-clinical testing. The non-clinical phase normally has 2-3 years of duration and its funding usually comes from venture capital firms (19). Although the overall process is generally represented as a series of sequential phases, in reality it is a continuum process with several feedback loops that trigger constant device's adjustments and new tests (20). In terms of clinical evaluation, usually innovative MDs are subjected to a first-in-man/pilot study i.e. a preliminary study to assess if a larger study is practical and to refine its study protocol. This "feasibility" study is then followed

by a pivotal study, which will involve more participants, and will generate the data needed to support the MD safety and effectiveness evaluation for its intended use.

However, the clinical evaluation process is dependent on the risk category of the device and it may not involve the execution of clinical studies (as it is explained below).

In contrast to medicines that generally stay in market for several decades, MD can be changed while in development and in average only takes 18-24 month to get a new and improved version of an already marketed device (4).

2.2.1. CLINICAL STUDIES – REGULATORY FRAMEWORK

While the European legal framework of medicines has been in place since middle 1960s (pushed by the thalidomide tragedy) a systematic regulation for MDs only appeared in the 90s. Before that each country had their own requirements: some countries had no regulatory requirements at all, others had published regulations only for certain type of devices (taking in account their perceived risk) while others classified/treated some MD as if they were pharmaceuticals products (21-23).

To facilitate trade within the EU single internal market, the EU has published a set of directives, known as the New Approach Directives and that cover a range of products, including MD. These measures intended to provide control on product design and above all, to seek for harmonisation regarding product safety requirements across Europe.

The main MD directives include: directive 90/385/EEC concerning active implantable medical devices (AIMD), directive 93/42/EEC, concerning MD in general and directive 98/79/EC concerning in vitro diagnostic devices. The Directives 90/385/EEC and 93/42/EC were amended by the Directive 2007/47/EC of the European Parliament and the Council of 5 September 2007 (21).

Besides the directives, there are other no legally binding documents, related with the conduction of clinical investigation that are worth mention:

- MEDDEV 2.7/4 – Guidelines on Clinical investigations: a guide for manufacturers and notified bodies: this document addresses considerations for the need to conduct a clinical study and their design (24);
- MEDDEV 2.7/3 – Clinical investigations: serious adverse event reporting: This document provides clarification for the reporting criteria for adverse events (24);

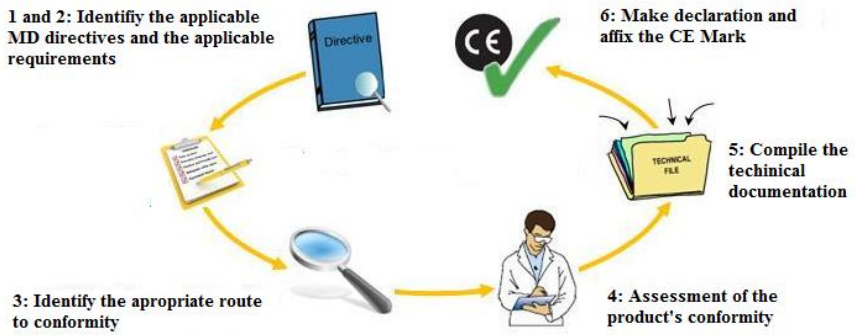
- International standard EN ISO[1] 14155:2011: provides practical guidance concerning the conduction and reporting of clinical investigations. Its consider the GCP equivalent for clinical studies (24).

On September 2012, the European Commission adopted proposals to revise the EU regulatory system for MD and that are expected to be adopted in 2014 and come to force in the period from 2015-2019 (25).

MD can been divided into four risk classes, according to their level of risk, from class I (low risk) to class III (high risk). The risk class is based on several criteria, such as the intended duration of use, degree of invasiveness and the body part affected (21).

Unlike what happens with medicines, the competent authorities are not responsible for assessing or authorising the entrance of a MD in the market. Instead, they can only be placed on European market if presenting the CE marking - a proof of conformity with the list of "essential requirements" defined in the MD directives. Custom-made MD and clinical research MD are exceptions, and do not need to bear the CE mark (figure 5) (21).

Figure 5 - The CE-marking process. Available from: CE-marking Association website(26).



It is the manufacturer's responsibility to perform the evaluation of conformity. However, for class I sterile devices or with a measuring function, and for class IIa, IIb and III devices it is required the intervention of a third party for the assessment of conformity - the Notified Body (27).

[1] International Organisation for Standarisation

The demonstration of conformity is based on "clinical data". Moreover, the recent amendment to the MD Directives establishes that all MD must have a clinical evaluation report in its technical file, regardless of its risk class (26).

This data can be originated from clinical investigation studies (the "clinical investigation route"), from a compilation of the relevant scientific literature (the "literature route"), or even from a combination of both (22). In general terms, active implantable, implantable and class III MDs require the conduction of a clinical study. Depending on clinical claims, risk management outcomes and on the results of the clinical evaluation, clinical investigations may also be required for non-implantable MD of classes I, IIa and IIb MDs (28) (table 1).

Table 1 – Clinical evaluation process for MD. Adapted from: LNE/G-MED North America website(24).

	Clinical evaluation Compulsory for obtain the CE Mark		
Risk level/product type	For MD with equivalent products on the market For class I, IIa, IIb non implantable MD Common used products	For MD with equivalent on the market that required further investigation. For class I, IIa, IIb and III	New, innovative MD with no market equivalents. Compulsory for class III MD and implantable devices. Can be considered for lower risk classes.
How to meet the requirements	Basic literature review	Advanced literature review to assess risk/benefit ratio	Robust clinical investigation to demonstrate a favourable risk/benefit ratio
Expertise required to meet goal	Medical writer	Medical writer, medical adviser and statisticians	Medical writer, medical adviser, project manager, patients and heath care professionals

2.2.2. CLINICAL STUDIES IN PORTUGAL

The MD directives were transposed to the national law by Decree-Law nr. 145/2009, June 17th. Decree-Law n. º 46/2004, of 19 August, relating to clinical trials, is also applied.

Contrarily to what happens with clinical trials, the pathway to obtain the approval for the conduction of a clinical study does not involve CEIC. Instead it begins with getting the ethical and institutional approval from each site involved; in parallel it is still necessary to obtain approval from CNPD. It is only after obtaining all these approvals that it is necessary to notify INFARMED about the intention of conducting a clinical study (29).

There is no available data about the number of clinical studies conducted in Portugal.

3. ACTIVITIES DEVELOPED

The main activity developed during my internship happed in the context of Blueclinical R&D business unit, and correspond to the management of a clinical study. Fortunately, I also had the opportunity to develop other activities in the other two company business units and attend to several meetings and training sessions that were very enriching and allowed me to develop and deepen some knowledge already acquired during the master's degree.

Unless otherwise specified, the activities were assigned to me by e-mail and were performed home-based.

3.1. GENERIC TRAINING

This section describes the different training sessions, visits and reunions attended during my training period, as well as the theoretical knowledge acquired during the same.

3.1.1. BLUECLINICAL'S QUALITY MANAGEMENT SYSTEM

In a training activity that took place in the phase I unit on 8th May 2013, I attend to a presentation about the company's QMS and some basic concepts regarding quality management.

A QMS encompasses four basis components: quality control (QC), quality assurance (QA), education/training and a set of clearly documented writing procedures.

QA is defined by the ICH E6-Guideline on GCP as *all those planned and systematic actions that are established to ensure that the trial is performed and the data is generated, documented (recorded), and reported in compliance with GCP and the applicable requirements* (30). QC comprises the operational techniques and activities undertaken within the QMS to verify that the requirements for quality have been fulfilled (31). In other words, QC is embedded into the operations, being integrated on the daily activities. QA, in contrast, is the responsibility of a department, independent of the operational units, sometimes may be even subcontracted to a third party, and it is focused on providing confidence that the quality requirements are being fulfilled (31).

The hierarchy and types of quality documents relevant to quality systems depends upon the company business objectives and model (31). Blueclinical's quality documents hierarchy is organised in three levels. The higher level is composed through the quality manual and the code of conduct. The medium level and low level are constituted by standard operations procedures (SOP) and supporting documents, respectively.

The quality manual describes the company QMS and the code of conduct consists in a set of principles issued by Blueclinical aiming to help their collaborators to conduct business with honesty and integrity. During the training activity mentioned above, all the Blueclinical's collaborators had the opportunity to give their input in terms of what they consider important to be present in the code of conduct.

SOPs are defined as *detailed, written instructions to achieve uniformity of the performance of a specific function* (30). In other words, a SOP specifies in writing who does what, when and how to perform a determined activity or process. The purpose is to ensure that every task is done in a consistently way by all the company collaborators involved (31). Ideally, they should be written by the people that will use them and the language must be clear and unambiguous. Its distribution must be controlled; this means that they must be reviewed before approval and release, any change must be re-evaluated and their distribution must be documented and controlled. When a SOP becomes obsolete, there should be procedures in place to prevent their use (31).

The supporting documents are documents used to complete/record a specific task, which can be described in a SOP or not.

Blueclinical's SOP for SOPs describes how the other SOPs/supporting documents must be written, their structure and format, the person responsible for the approval and the periods for revision. It has also a template for the construction of a new SOP as an appendix (32).

SOPs along with other relevant quality documents ensures the effectiveness and efficiency of quality systems (31).

Having all the above in mind, SOPs are excellent training tools when starting a new job position in a clinical research company.

3.1.2. BLUECLINICAL PHASE I

During my training I had the opportunity to visit the phase I unit several times while it was in construction and to observe to some of the processes that were necessary to adapt and equip the space conveniently. Moreover, on a training activity that took place on 8th May, I had the opportunity to visit the unit already finished and practically equipped and to meet the investigational team. Along the way, I tried to understand and discover more about phase I trials and available guidelines for phase I units.

According to the Association of the British Pharmaceutical Industry guidelines, a phase I unit must have the enough space to conduct the planned trials (7). Also, and to allow an appropriate risk

management, the units must be located close to/ in a hospital with acute/emergency settings or an intensive care unit (7). An alternative is to have the required equipment to ensure cover for medical emergencies by itself.

In terms of facilities, Blueclinical's phase I unit has:

- 11 bedrooms (4 double, with private bathroom, and 7 triple). The rooms are equipped with beds on wheels, adjustable for height and tilt. The furniture's distribution was planned to allow moving medical equipment in the rooms. As subjects must be under supervision of the staff personnel while inside the room, the rooms have windows directed to the corridor;
- A separated office for medical examinations, in order to ensure the required privacy;
- A pharmacy. This room has restricted access only for authorised staff and has the adequate conditions for the drug supplies (e.g. temperature and humidity control/recording, and protection from direct light);
- Laboratory, with appropriate equipment for processing and storage of the biological samples;
- Living and dining room;
- Two work offices;
- One room for sample collection;
- A room with lockers for the volunteers to save their belongings;
- A room for the computer server;
- Staff's locker room;
- Male and female WC's and showers;
- The unit has controlled access, and there are synchronised clocks distributed in the corridor to guarantee that the team elements are coordinated.

The unit functioning is also assured by support services that are provided by Hospital da Prelada, namely security, alimentation, cleaning and laundry, and emergency services.

Phase I trials include a range of studies, namely:

- First-in-man trials - consist in the administration of single ascending dose in order to get insight in terms of the drug tolerability, safety, PK and pharmacodinamic (if possible).
- Subsequent trials – that include:
    - Multiple ascending doses;
    - Trials to evaluate the potential influence of food, concomitant medication, gender, age and genetic differences on the activity of the drug candidate;
    - Trials to assess the dose/concentration-activity relationship;
    - Evaluate the PK of radiolabelled IMPs;

- Bioavailability (BA) or bioequivalence (BE) trials;
- Assess the effect of the IMP on the QT interval (7).

Generally, these trials are conducted in healthy volunteers, from both genders and older than 18 years. Healthy subjects are generally easier to find and not taking concomitant medicines increases the probability of an uniform response (7). In other words, it helps separating the effects caused due to the study intervention from those caused by any disease/medication that patients may have taken or may be taking. Trials for IMPs that present serious risks, such as potential oncologic drugs are conducted in patients (33). The total number of subjects included varies with the study drug and study type, but it generally ranges between 20 and 80 participants (7).

Regarding the subject recruitment methods, Blueclinical's website has a specific tab where the potential volunteers can complete an online form. Since the website collects subjects data and may be considered a mean of advertisement its content was evaluated and approved by CNPD and CEIC. Other methods used worldwide include advertisements in newspapers/magazines or on notice boards, radio, commercials on TV/websites or by recommendation from others. Regardless of the recruitment method used, the subjects must be capable of voluntarily providing valid consent and should be properly informed and clarified for any questions they have (7).

The health status of the volunteers is judged during the screening activities. Blueclinical's staff contacts by telephone the potential candidates i.e. those registered in the website's database, and provide them with trial-related information (e.g. study design and duration, IMP's characteristics, possible adverse events, etc.). If the subject is still interested a medical evaluation must be conducted at the phase I unit facilities. This visit will include signing the informed consent form (ICF) and then recording the patient medical history, performing a physical exam and conducting a series of blood and urine analysis, like testing for drugs of abuse, HIV, hepatitis B and C and also pregnancy test in women with child-bearing potential. Depending on the trial specificities, other exams may be needed.

After reviewing all the results from the screening visit procedures the subject is informed if he is eligible to participate or not. During this process he can decide at any time to decline participation.

Lab analysis is required for safety reasons and for PK (bioanalysis). In both cases, sample collection and preparation is performed at the phase I unit. Safety analysis is performed at Hospital da Prelada. These analysis usually are conducted during screening, but also at admission, medical discharge and during the follow up period. Bioanalysis performed by Anapharm Europe lab, at Barcelona, Spain.

As these trials usually have non-therapeutic objectives, the study participants are normally compensated for their participation. The value for compensation must be previously approved by CEIC and must never be proportional to apparent risk (34).

In terms of regulatory/ethical approval, phase I trials follow the same principles as all other studies, and, in Portugal, require the approval from the relevant ethics committee (CEIC) regulatory agency (INFARMED) and CNPD.

This journey was very enriching and gave me a valuable insight about the logistics and the organisation of a phase I unit.

3.1.3. BLUECLINICAL SMO

During this 9 month period I attended to two training sessions regarding Blueclinical's SMO mission and strategy. I also had the opportunity to be present on several meetings where the SMO service was presented to several medical investigators. Those meetings happened with three main purposes: to present Blueclinical, to assess the investigators interest in having a CSC on the investigational team and last, to collect information about their main interest in terms of therapeutic areas for conducting new clinical trials.

The referred training sessions along with the meetings attended allowed me to develop a deeper knowledge about the nature of a SMO service, the role of a CSC and the dynamics of a clinical site, which I present below.

A SMO is an organisation specialised in providing clinical trial related services to clinical sites (1). As referred, the purpose of Blueclinical SMO is to improve the capacity of the Portuguese sites to carry over clinical research activities. This objective is accomplished by placing fully dedicated and highly qualified clinical CSC in the institutions, who will be integrated onto investigational teams and take on meaningful assignments in the conduction of the clinical research.

Until the middle 1970s CSC positions were rare, but since then they have been increasing in number. Currently a research team includes the PI, sub investigators, nurses, pharmaceutical services and technicians. In some sites it also is the figure of the CSC. While the responsibilities of the investigators, sponsors and clinical research associates (CRA) are well established in the Portuguese law for clinical trials and in the GCP guideline, the same does not happen for CSC (35).

The purpose of Blueclinical SMO is for their CSCs to develop a deep knowledge about the study protocol, including the inclusion and exclusion criteria, study procedures and timelines,

assuming responsibility for coordinating the daily clinical trial activities, since the beginning until the study conclusion.

The general responsibilities of a CSC include:

Pre-study activities: Before the study start, the CSC assists the PI in the completion of the feasibility questionnaires[2] that are received from different CROs and sponsors. Following that, and if the sponsor/CRO decides to perform a pre-site selection visit, the CSC is also responsible for accompanying the CRAs and answer to all of their questions. If the site is selected, CSC will became the point of contact with the sponsor and provide all the necessary documents (e.g. templates available, study team CVs, etc.) for the study submission to the national/local ethics committee.

Study activities: CSC often collaborate with the PI in communicating the study requirements to the other team members (internal training). They also participate in the informed consent process, helping the investigators communicating the study information to patients and by assuring that the correct version of the ICF is being used, and it is timely and appropriately signed and dated.

During the study conduction, CSC are responsible for preparing and scheduling the study visits. During these visits, they must assure that all the medical data/ biological samples are collected according with the protocol and they also can take responsibility for administering the study questionnaires to patients, when required. In the case of adverse events they must also collect and register all the relevant information. After completion of the entire visit procedures CSC have to enter data in the case report forms (CRF), perform drug accountability and calculate treatment compliance. Between visits, they must assure adequate inventory of study supplies and maintain the study files organised according to sponsor's requirements.

During the study conduction, routine monitoring and auditing visits should be expected. CSC must prepare the study files for these situations and then collaborate with the PI to respond to any audit/monitoring findings by implementing the necessary corrective measures.

Closeout activities: When a study ends, CSC must assist the PI in the submission of all the necessary closeout documentation. They will also collaborate with the trial's CRA to arrange a secure place for the study documents, always in compliance with the site procedures and the contracted length of time.

Having this description in mind, it is clear that hiring professionals specifically dedicated to clinical research has an undeniable influence in improving the efficiency and productivity of the research centers. However, along the way I realised that many of the investigators to whom

[2] Questionnaire intended to assess the suitability of a certain site to conduct a study, i.e. investigator qualification and experience, existence of experience clinical staff and adequate infrastructures, etc.

Blueclinical SMO service was presented were not familiar with the role of the CSC, while others associated this role to purely administrative tasks, which is a much diminished vision about the role of a CSC**.**

Besides this, Blueclinical SMO also intends to organise and maintain the institution's quality system for clinical research, to train and certify the staff in GCPs and to actively seek for new sponsors and new studies to implement in the institution.

3.2. MAIN ACTIVITY – MANAGEMENT OF A CLINICAL STUDY

As an associate project manager, I formally belong to the Blueclinical R&D business unit.

As already stated in the "host company overview" section, one of the services provided by Blueclinical R&D consists in obtaining regulatory approval for clinical trials/studies. During my training period, Blueclinical was contracted by an international sponsor to implement a clinical study with an AIMD (i.e. medical device whose function depends on an electric source of energy that is not generated by the human body/gravity and that is intend to be totally or partially introduced into the human body and remain after the procedure (21)) in five national sites. The study was already on going in other countries and Portugal was included as a rescue country to achieve the recruitment targets.

The process of obtaining all the regulatory authorisations and approvals needed for initiating a clinical study is commonly classified as "pre-study activities".

When this task was assigned to me, the first step was to carefully read the master service agreement (MSA), the sponsor's procedures and the study documents. I also had to get familiar with the applicable legislation.

The majority of the documentation can be submitted in English. However, the ICF, information for patients and the clinical investigational plan (CIP) synopsis must be written in Portuguese.

My first activity was to perform the translation of the CIP synopsis to Portuguese and check the accuracy of the ICF translation. The translation turned out to be quite challenging, due to the several technical/medical terms used, which required some research.

In Portugal, and as already referred, a clinical study with an AIMD requires the approval of the following entities: local ethics committee (CES) of each site involved. AB of each site involved, CNPD and INFARMED.

3.2.1. OBTAIN ETHICAL AND INSTITUTIONAL APPROVAL

The minimum information requisites when submitting a clinical study for evaluation by the local ethics committee is established in the INFARMED deliberation no. 514/2010 (36). However each ethics committee has its particularities and in spite the basis for their work is the same deliberation they have different requirements amongst themselves.

Having this in mind, the first step was to contact with the research sites to obtain information about any specific documentation required and to understand the evaluation pathway within each site.

The documentation required included, in general terms, the following:

- CIP and a CIP synopsis in Portuguese;
- Cover letter;
- Investigator brochure;
- CRF;
- ICF and information for patients;
- Authorisation from the head of the department;
- Authorisation request to the ethics committee president;
- Study team's Curriculum Vitae (CV);
- Ethics committee's specific questionnaire/form;
- Authorisation request to the AB president;
- CNPD authorisation;
- Insurance policy;
- Clinical site agreement (CSA)/financial protocol.

For the purpose of tracking the retrieval of mandatory documentation, I created a template/checklist, which I updated for each site whenever there was new information available. This tool turned out to be extremely helpful to organise my work more efficiently. Whenever a site did not have a specific template available for the authorisations request, I had to create one to propose them, which ended up being quite a frequent approach as most sites do not have standard operating procedures or forms.

The topics covered by the ethics committee questionnaire were similar for all the sites and included:

- General information about the study: study objectives, study design, other national sites involved.
- Study population: who is the target study population? How will the informed consent be obtained?
- Information about the data to be collected, the methods for collection and how the data's confidentiality/patient privacy is ensured.
- Risk-benefit: what are the expected benefits and risks/inconveniences for the study participants?
- Planned payments to patients: will the patients be reimbursed by travel costs? In case of damage caused, is any compensation planned?

The CSA is a legally binding document used between the sponsor and the clinical site that establishes the terms and conditions associated with the conduction of a clinical study (e.g. insurance/liabilities, intellectual property/publications, payment, data protection, safety reporting, etc.) (37). The execution of the CSA is often viewed as one of the main reasons for delays in a study start up. Although the sponsor had provided us with an already prepared CSA (sponsor's template), some sites had their own financial contract templates that had to be followed. As a strategy, and to facilitate both the site and the sponsor's agreement, site templates were included as an "appendix" to the sponsor's CSA, from now on referred to as financial protocol.

The completion of those templates involved the following general steps:

- Identify all the medical procedures/exams required as per the CIP.
- Calculate the indirect costs (e.g. medical procedures/exams costs, patient expenses reimbursement). The calculation of the amount due for medical procedures/exams required consulting Portaria no. 839-A/2009, that determines the prices to be charged according to the national health service price tables, and Ordinance no. 306-A/2011 regarding patient fees.
- Calculate the direct costs (i.e. payments to the investigational team). This activity involved close contacts with each site's PI to get the amount due to the whole investigational team divided by the different team elements.

Prior to the submission per se, all sites performed a pre-evaluation of the financial protocols. Thus I had to prepare a draft version of the CSA/financial contract, which was submitted for site's revision and approval. The entity responsible for performing this pre-evaluation differed from site to site (e.g. pharmaceutical services, the hospital financial department or the investigational center).

In order to be more effective in my work, I have identified a point of contact at each site to whom I resorted to follow up the process or to request for clarifications. Due to the particular

characteristics of the study design – the randomisation of the study patient occurs during his hospitalisation – the site often raised questions that had to be promptly addressed by me.

After collecting all the information needed and preparing the submission dossier, I arranged a meeting with the PI/CSC for collecting all the missing signatures and for hand delivering the dossier to the ethics committee.

During this process I was challenged to elaborate a writing procedure about the submission process in each site. The purpose was to create a document that would facilitate the work of other Blueclinical's collaborators when dealing with the same sites in the context of a clinical study submission. At the same time, this task turned out to be a good systematisation exercise.

3.2.2. CNPD APPROVAL

According with the Law 67/98 from October 26th it is mandatory to submit and get approval from CNPD for all the clinical studies/trials that involve the management of personal data and/or sensitive personal data(38).

The submission is performed electronically via an online form – the general notification form. The information requested by CNPD includes:

- Type of data collected and method for collection i.e. direct or indirect collection;
- Period for data storage;
- Security measures implemented for data protection;
- Existence of interconnection of data (e.g. when there is a possibility of correlating data in a file with data from other files kept by the same or others parties) (38);
- Existence of transmission of data to outside the Europe/European Economic Area;
- How the right of access is ensured.

Due to the specifics of the information requested by CNPD, the completion of this form required a close contact with the sponsor.

After the electronic submission, the applicant receives instructions on how to pay the fee and an e-mail is sent to CNPD to conclude the submission process. The e-mail I sent included the following attachments: copies of the application form, the ICF, the CRF and the CIP synopsis. Sending the CIP is a common strategy as it provides additional detail that can avoid the number of CNPD additional questions, thus avoiding delays in the approval process.

CNPD has no legislated deadline for issuing its authorisation. However, on average, it takes 2 to 3 months.

The CNPD submission was done in parallel with the submissions to the study sites as a strategy to save time. For this, I had to include in every submission dossier the following: a statement of commitment (signed by the sponsor) to not initiate the study before obtaining all necessary approvals, a copy of the submission form and the fee payment proof. When the authorisation was issued, I entered in contact again with the local ethics committee to provide a copy of the CNPD approval letter to complete the submission dossier.

3.2.3. INFARMED SUBMISSION

While the process was under evaluation by the ethics committees I started preparing the INFARMED submission. According to the national legislation, for class III, implantable, and invasive for long term use class IIa or IIb MDs, the manufacturer can initiate the clinical study 60 days after the notification to the competent authority. For other devices the clinical study can initiate immediately after INFARMED notification (29).

The INFARMED notification involves submitting the same documentation included in the submission dossiers to the sites plus the ethical approval letters/AB authorisation letters already issued, the approved and signed financial protocols and the device's labels. Additionally, it is necessary to have the "Statement of Clinical Investigation with AIMD" and the "Form for AIMD in Clinical Investigation", both available at the INFARMED's website, completed and signed by the sponsor (39).

Regarding the device's label, the national legislation has clearly established requirements (numbers 17, 18, 19 of Annex X) (40). In this context, I had to analyse the device's documentation, to check for compliance with the national requirements and to perform the necessary adjustments. This analysis and sharing it with INFARMED allowed the sponsor to get a waiver on the translation of the full label into Portuguese, i.e. a simplified label has been authorised thus speeding up the submission process.

In contrast with what happens with clinical trials for which there are clear indications about the format for the application to INFARMED, there is no information available on the required submission structure for clinical studies. For this reason I had to create a structure, which was based on the "instructions for applicants" for clinical trials that are available at the INFARMED website.

The submission to INFARMED was made in a mixed format (paper and CD–ROM), by regular mail.

3.2.4. STUDY PRESENTATION TO OTHER POTENTIAL INVESTIGATORS

In the middle of the regulatory submission to the selected sites I had the opportunity to perform a study presentation to Investigators from a new site. The purpose was to assess their interest in participating.

During this 9-month period, four out of five of the sites selected approved the study, as well as CNPD and INFARMED.

In the end I had to organise all the submitted study documentation along with all the relevant correspondence per site and provided to the sponsor. Also, all the approval/opinion letters and the correspondence selected had to be translated to English by me.

3.3. OTHER ACTIVITIES

In parallel with the activities described in the previous section, I engaged a series of other activities described below.

3.3.1. WRITING PROCEDURES

Taking my curricular training in a new-born company gave me the opportunity to draft several SOPs and the respective forms, namely:

- Site initiation visit
    - Template for a site initiation visit report
    - Patient enrolment and identification log
    - Delegation of tasks to study Staff
    - IMP/ MD release
    - Site visit log
- Routine monitoring visits
    - Template for a monitoring visit report
    - Screening log

    - Enrolment log
    - Contact report form
    - Close-site visits
    - Template for close-site visit report
    - Record retention form
- Trial Master File (TMF) (referred on page 30)
    - Archive index/log
    - Documents track
- Clinical study submissions (referred on page 25)

The sources of information used include, obviously the Blueclinical's SOP on SOPs, but also the applicable regulations and guidelines and any available technical informational, like published handbooks and manuals.

In the middle of the process the company decided to readapt their SOPs, opting by a new, simpler and more intuitive SOP structure. I had to adapt the following SOPs according to a new SOP template:

- ICF
    - ICF template
    - ICF QC checklist
- Compensation to healthy volunteers
    - Request for compensation for healthy volunteers
    - Payments control
- Phase I clean-ups
- Phase I uniforms
- Selection and training of medical investigators

3.3.2. PREPARATION OF A NATIONAL SITE IN THE CONTEXT OF BLUECLINICAL SMO

During the last year, Blueclinical SMO has established a protocol with some national hospitals and during my training period I had the opportunity to spend two weeks in one. I went together with a Blueclinical's collaborator that was doing her professional training as an associate CSC.

The site where I had the opportunity to work had never had a CSC. The CSC activities described in the "generic training" section have been done by the study nurses, the investigators or the investigational center coordinator.

My stay on that hospital happened with the purpose to characterise the hospital performance in terms of clinical research during the past five years. For that, I have been involved with:

- **Revision of the TMF** – The TMF consists in the study's essential documents, which allows the evaluation of both the trial conduction and the quality of the data produced (30). The revision of the study documents included checking for discrepancies or missing documents.
- **Clinical trials/observational studies database construction** - The information collected included: type and number of studies (e.g. clinical trial vs. observational study) and their status (e.g. ongoing vs. concluded), therapeutic area concerned, investigators involved and their contacts, sponsor identification, recruitment rates (number of proposed subjects vs. recruited subjects), payment per patient and responsible CRA and their contact.
- **CV collection** – the collection of a signed, dated and updated version of all the investigational team members CVs is often a limiting step when trying to submit a new clinical trial. Having said that, I collected all the CVs already available and prepared a new draft version according to a new standardised format.
- **Elaboration of a financial report** – Using the data collected, I wrote a draft version for a financial report, which included payments performed for every industry-sponsored study, per year, distinguishing between clinical trials and observational studies. I also compared it with the value that would have been received if the investigator was able to accomplish the recruitment target.
- **Writing procedures** - it is also Blueclinical's responsibility to outline the quality manual for clinical investigation and also all the relevant procedures. In this context, I wrote a draft version for a procedure concerning the organisation and maintenance of the TMF, both and English and Portuguese (already listed above).

These activities allowed me to contact with different study documents from different sponsors as well as to contact with the day-to-day activities of a national investigational center. Additionally, it allowed me to work with new colleagues. For these reasons, I consider it a big learning opportunity.

3.3.3. BIOEQUIVALENCE TRIALS - LITERATURE RESEARCH

A BE study works as a proof of the clinical effectiveness and safety of a generic drug since it is scientifically accepted that if the blood concentrations of the active ingredient of two drugs are the

same, their concentrations at the site of action are the same and their clinical behaviour will consequently be the same (41). Two drug products are considered bioequivalent if there is no clinically significant difference in their BA. BA is the measurement of the *rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action*(42). It is assessed through three PK parameters: area under the curve (AUC), peak concentration (C_{max}) and time to reach C_{max} (T_{max}) (41).

As any other trial, a BE trial needs to be described in a scientific and ethically sound study protocol. When designing the study it is essential to spend some time analysing the applicable regulatory guidance and collecting detailed information about the brand product(42). In this context, I was asked to conduct a literature search to compile relevant PK information for a set of marketed drugs, including:

- C_{max} and t_{max} - gives information to correctly distribute the sampling collection points.
- Drug's half-life ($t_{1/2}$) - provides information about how long it is necessary to collect samples.
- C_{max} and AUC's intra-subject and intra-individual variability.- gives information regarding the number of subjects required. The intra-subject refers to the variability that it is observed when repeating the same experiment on the same subject and under the same conditions; the inter-subject variability is the variability observed in different subjects under the same experimental conditions (43).

The sources of information consulted included the approved summary or the product characteristics, and related scientific papers available.

This activity allowed me to review concepts already learned during the master's degree.

3.3.4. QREN APPLICATION

During my training period, I had the opportunity to write some texts for a QREN's application. QREN stands for Quadro de Referência Estratégico Nacional and *it constitutes the framework for the implementation of the community's policy on economic and social cohesion in Portugal in the period of 2007 – 2013*. In simple words, it is a reference document that presents the country's strategy and the themes chosen for the structural funds (Fundo Social Europeu and Fundo Europeu Agrícola de Desenvolvimento Rural) and the Cohesion Fund's intervention) (44).

Bearing in mind the different characteristics of the different companies that constitute our national economic environment, three incentive systems were established: the System of Incentives

for Research and Technological Development, the System of Incentives for Innovation, and the Incentive System for Qualification and Internationalisation of small and medium enterprises (44).

The presentation of applications to the different incentive systems happens by contests that are open through the publication of the Notice of Opening, in Portuguese "os Avisos de Abertura". These notices establishes the contests' objectives and criteria, deadlines for application's submission, methodology for the determination of the project's merit/score, budget for incentives granted and what expenses are eligible/illegible (44).

The projects received are then sorted in descending order according to the project's merit and until the budget limit established in the Notice of Opening is depleted. In case of equivalence the criterion for distinction is the date of application.

When I engaged this task I attended to a meeting with the person responsible for that kind of projects where I had the opportunity to participate in sorting the most appropriate contest for a company having Blueclinical's characteristics.

The application form is available online. The information required included, among others:

- Company's history/evolution;
- Company's general information (e.g. address, zip code, URL, share capital, date of start of activities, etc.);
- Company's staff and respective level of qualifications;
- Justification of the project's inclusion in the selected contest;
- Description of the services provided;
- Auto-analysis of the project's merit and justification according to the criteria established in the Opening Notice.

3.3.5. DATABASE CONSTRUCTION

In parallel with the activities already described, I engaged other smaller tasks that although may have taken a smaller part of my time, were also interesting challenges:

- Microsoft Office Excel database construction concerning marketed in-vitro MD and their functions.
- Information collection concerning national hospital centers, the population served and the respective clinical directors and their CVs, when available. The purpose of this information was related with the Blueclinical SMO business unit, since Blueclinical is searching for new hospitals to established new partnerships.

3.3.6. TRANSLATION ACTIVITIES

Besides the study documentation/correspondence already referred, I also performed the translation of two different models of confidentiality agreements.

4. DISCUSSION

4.1. DIFFICULTIES FELT AND STRATEGIES USED

First of all, I have to refer that having the opportunity to work with a clinical study constituted a very interesting challenge, mainly for two reasons: my academic background was always more directed to clinical trials, and while there is already established procedures and a good level of knowledge of the procedures in place with clinical trials, the same does not happen with clinical studies.

In fact, when I contacted the sites, only one had a prepared list for clinical studies; the other sites provided us with information available for clinical trials or observational studies instead. In order to overcome this issue, I had to prepare and add to the submission dossier a document that briefly explained the legal framework applicable to clinical research with MD.

Working with five sites at the same time, obliged me to deal with lots of different documents, deadlines and persons. Also, I had to create my own "project management tools":

- **Contact report form** – it consisted in a simple Microsoft Office Word document where I registered the name of the person I have contacted, the contact date and a summary of the conversation taken/follow-up actions agreed. This "tool" was especially useful at the beginning, when I wasn't completely familiar with the procedures in place at each site.
- **Issue management log** (table 2) - The purpose was to create a document where I could register every problem that occurred. I ended up registering also the different study tasks/steps for each site and the respective status. This allowed me to have the situation under control, ensuring that nothing was forgotten. Moreover, the document turned out to be very useful when I had to provide the sponsor with the project status reports.

Table 2 – Issue management log layout

Site	Description	Open date	Close Date	Status	Comments	Priority
Site X	Xxxx			Open		
Site Y	Xxxx			Closed		

- **Purchase order log** (table 3) – it consisted of an Microsoft Office Excel spread sheet that allowed me to associate the sponsor's work orders and the respective purchase orders' number with a description of the different services performed by Blueclinical, their status and the date of conclusion.

Table 3 – Purchache order log layout

Work Order	Purchase Order	Activity	Value	Payment done: add date Payment pending: pending	Invoice number	Tasks Status
#1	XXX		xx €	Pending		done
#2	YYY		xxx€	XXMAY2013		pending

Still related to project management, I also highlight the importance and the challenge that communication represents. This even gets more complex in the context of international teams, when all the parties use English to communicate and this is not anyone's native language.

During this process, I had to be obviously in straight contact with the sponsor and with the selected sites, including PIs, CSCs and the services responsible for the financial protocol evaluation.

The main technique used for communicating with the sponsor was the e-mail. The main reasons for communication included: request for additional information/documents (as each sponsor's study team member had a clearly and defined role, I had to enter in contact with different persons, from different departments), agreed weekly study status updates or even invoicing matters. There were periods when this contact happened on a daily basis, because the sponsor was constantly requiring clarifications about the national requirements. Since project management is an activity very much sensitive to timelines, it was also quite demanding to manage sponsor's expectations at that level.

The main techniques of communication used with the sites were the telephone contacts and the e-mail; face-to-face visits have also been performed. In order to get faster responses I monitored the approval status, at least, on a weekly basis with each site.

Since I have been strongly encouraged from the beginning to be autonomous, I also contacted INFARMED directly whenever required to obtain clarifications needed across the whole process.

In the beginning, all my e-mails were pre-evaluated by a superior, however in the middle of the process I gained autonomy at this level and started communicating directly with the sponsor and the national sites.

Writing the texts for the QREN's application was other task that also occupied a considerable percentage of my training period. The main difficulty felt in this task was not directly related with writing the texts, but instead in understanding the regulatory framework involved, that was full of concepts that were unknown to me. Nevertheless, I was very pleased for having had this opportunity since it allowed me to deal with a subject that was completely unfamiliar to me.

Regarding the SOPs, one of the main difficulties that I felt during this task was to find a balance between writing a short SOP, so the reader does not lose interest, but at same time not forgetting any important information.

4.2. LEARNING OUTCOMES

During this 9 month period I have developed a deep understanding of the national legislation for the conduction of clinical studies. I learned how to construct and organise submission dossiers and I am now also able to notify a clinical investigations with MD to INFARMED and to perform a submission to CNPD. I have also developed some knowledge on business documentation (e.g., MSA, work and purchase orders and invoices) and I dealt for the first time with financial protocols.

This experience also made me testify that there is no place for disorganisation and lack of rigor in this setting. Documents must be controlled and the submitted versions must be identified and recorded. The quality of the documentation submitted makes the difference between a timely approval and a lengthy one, caused by unnecessary delays due to successive clarification requests.

Although I did not had the opportunity to perform any monitoring activity, I elaborated three SOPs regarding the three types of monitoring visits and the respective supporting documents, what allowed me to learn more about this subject and to clarify some misconceptions that I had.

I also gained a very useful insight about the logistics and function of a phase I unit and the dynamics of phase I trials, as well as good level of understanding regarding the QREN's regulatory framework and the submission of applications.

While the main hard skills gained during this process become clear by simply reading this report, there are several soft skills that I definitely had the opportunity to develop/improve during this experience.

Developing the majority of the described activities home-based definitely contributed for improving autonomy, organisation, time management skills and critical thinking. During this period I was confronted with several new situations that I had to overcome by reading and interpreting the legislation in place and by seeking for clarifications contacting directly the entities involved. In terms of time management, I learned to prioritise my tasks and began planning my days on the day before. This way I ensured that nothing was left behind and things were done quick and efficiently.

The improvement of my writing/communication skills was something that becomes visible to me during the process. My e-mails became clearer, shorter and objective which consequently made communication more easy and effective.

Looking back, it is very clear to me that my academic journey at University of Aveiro was essential for concluding with success the described activities. Since the beginning of my academic journey I have been strongly encouraged to be autonomous, to develop a strong critical spirit and to work in teams. The development of these skills started during the bachelor degree thanks to the teaching methodology used that confronted students with real life situations that had to be solved by studying at home. There is no doubt that the teaching method made a huge difference in terms of being prepared for facing new situations.

The Master's degree also offered me the opportunity to collaborate with the University's Clinical Research Office. This started during my 1st year in the Master and continued in parallel with my training period at Blueclinical. It gave me the opportunity to work on the submission of some observational studies to several national centers and to CNPD, which was also a good preparation for the activities I had to develop during my training period. Although the process of submitting an observational study is much simpler than the process of submitting a clinical trial/study, there is no doubt that the previously mentioned experience constituted a tremendous advantage. Moreover, I integrated these projects always as a project manager, which allowed me to develop other competencies as leadership, motivation and communication skills.

I also cannot fail to reflect about the opportunities and disadvantages of taking an internship home based and in a newly created company. Some of the positive points were already mentioned: I had the opportunity to help constructing the company's QMS by drafting several versions of writing procedures; I assisted to part of the process behind starting a phase I unit and I was challenged to write some texts for a QREN's application. I had to do this by trying to be autonomous during the whole process.

Unfortunately I cannot help to recognise some "disadvantages". As Blueclinical was just starting their activities, I only had the opportunity to participate in one project in the context of Blueclinical R&D business unit. I also did not have the opportunity of experiencing to work in an "office environment", which I believe may be a contributing factor for "professional growth" when a student first leaves the academic setting.

Nevertheless, I truly believe that I took the best of the opportunities I was given and I know that if I had the opportunity to repeat all the activities again I would do it in a much more professional and effective way.

5. CONCLUSION

This report presented the activities developed during my training period at Blueclinical Ltd, as well as the skills and learning outcomes achieved.

During this 9-month period, I had the opportunity to experience the real work environment, as well as to test knowledge and improve competences that I had being developing during my academic journey.

The main activity developed involved obtaining all the necessary regulatory approvals to initiate a clinical study in five national sites. I am very glad to have had this opportunity, since it allowed me to deepen my knowledge about the MD sector. At the same time it was a challenge due to the clear lack of knowledge of the procedures in place regarding clinical investigation with MD.

Taking my curricular training in a company with three distinct and innovative business units was also a great advantage. I had the opportunity to learn about the functioning of a phase I unit and also to spend some time in a national hospital, dealing with different study documents and contacting with new people.

I overcame my difficulties by studying the procedures in place and searching for solutions and new strategies to organise myself and my work. I believe that my academic background provided me with a range of soft and hard skills that were essential for an easier adaption to the work environment and integration into the working teams. I am talking about autonomy, problem solving capacity and better communication skills but also about valid knowledge with real applicability in the work setting.

Finally, I want to referrer that I am very thankful for having had the opportunity to integrate a company like Blueclinical, with clear innovative services on the national clinical investigation field, and to watch their growth during the last months. It was an incredible experience and a great place for experiencing my first contact with the work environment.

6. *BIBLIOGRAPHY*

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