Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2014

CATARINA MANUEL SOUTO MORAIS

RELATÓRIO DE ESTÁGIO CURRICULAR NA BLUECLINICAL LDA.
Curricular Training Report 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 do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro e da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical Lda.

“Deem-me um ponto de apoio e eu moverei a Terra.”

Arquimedes

o júri

Presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático da Universidade de Aveiro
Arguente	Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta da Universidade de Aveiro
Orientador	Doutora Cristina Manuela Pinto Vieira Lopes Diretora de Operações Clínicas da Blueclinical Lda

agradecimentos

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A todos, obrigada por me fazerem feliz!!

palavras-chave Coordenadora de Investigação Clínica, Ensaios Clínicos, Blueclinical

resumo

Este relatório descreve as atividades que desenvolvi e as aprendizagens que adquiri durante o meu estágio curricular, enquanto Coordenadora de Investigação Clínica na Blueclinical – Investigação e Desenvolvimento em Saúde, Lda.

O estágio curricular foi realizado no âmbito do segundo ano do Mestrado de Biomedicina Farmacêutica da Universidade de Aveiro.

A principal atividade desenvolvida foi a coordenação de ensaios clínicos no Centro Hospitalar Vila Nova de Gaia/Espinho, desde as fases mais iniciais do seu desenvolvimento – questionários de exequibilidade – até às fases mais tardias – visita de fecho. No entanto, pertencer a uma empresa ainda em processo de criação foi uma mais-valia pela pluralidade das tarefas efetuadas, incluindo tarefas relacionadas com gestão, criação do sistema de gestão de qualidade, entre outras.

Durante o estágio foi-me possível tomar conhecimento das dificuldades encontradas durante a criação e implementação de um Gabinete de Investigação Clínica e também aperceber-me de algumas diferenças entre o mundo académico e o mundo profissional.

Para além da descrição das atividades desenvolvidas e dos objetivos que me propôs a atingir, este relatório tenta contextualizar o estágio na estrutura da Blueclinical e no estado de arte da investigação clinica. É também apresentada uma análise crítica dos pontos fortes, pontos fracos, dificuldades e oportunidades encontrados durante o estágio.

keywords Clinical Research Coordinator, Clinical Trials, Blueclinical

Abstract

This report describes the activities I have developed and the knowledge I have acquired during my curricular training as Clinical Research Coordinator at Blueclinical – Investigação e Desenvolvimento em Saúde, Ltd.

The curricular training is part of the second year of the Master's Degree program in Pharmaceutical Biomedicine University of Aveiro.

The main activity developed was the clinical trials coordination at Hospitalar Center Vila Nova de Gaia/Espinho, since the earliest phases – feasibilities – until latest phases – close-out visit. Nevertheless being part of a recent company, still in creation phase, was a positive aspect as it allowed me to perform a large variety of tasks, including management, creation of the quality system, among others.

During the internship I was able to acknowledge the difficulties faced while creating and implementing a clinical research office, as well as acknowledge some differences between the academic environment and the professional environment.

Besides the description of the activities developed and the objectives, this reports intents to contextualize the internship in Blueclinical's structure and in clinical research state of art. It is also presented a critical analysis of the strengths, weakness, opportunities and threats faced during the curricular training.

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LIST OF ABBREVIATIONS

AE	Adverse Event
COD	Clinical Operations Director
CEIC	*Comissão de Ética para a Investigação Clínica* (Portuguese Ethics Committee)
CHBV	*Centro Hospitalar do* Baixo Vouga (Hospital Centre of Baixo Vouga*)*
CHCB	*Centro Hospitalar da* Cova da Beira (Hospital Centre of Cova da Beira*)*
CHTV	*Centro Hospitalar de* Tondela-Viseu (Hospital Centre of Tondela-Viseu*)*
CHVNG/E	*Centro Hospitalar de* Vila Nova de Gaia/Espinho (Hospital Centre of Vila Nova de Gaia/Espinho*)*
CPI	Critical Path Initiative
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRM	Clinical Research Manager
CRP	Blueclinical Clinical Research Partnership
CV	Curriculum Vitae
e-CRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
GAGIC	*Gabinete de Apoio ao Gabinete de Investigação Clínica* (Supporting Office to Clinical Research Office)
GCP	Good Clinical Practices
GIC	*Gabinete de Investigação Clínica* (Clinical Research Office)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde I.P* (National Authority of Medicines and Health Products)
IWRS	Interactive Web Response System
NME	New medical entity
PBL	Problem Based Learning
PHI	Blueclinical Phase I
PI	Principal Investigator
R&D	Blueclinical Research and Development or Research and Development (context dependent)
SAE	Serious Adverse Event
TMF	Trial Master File

1. INTRODUCTION

The present work intends to report the activities developed and experience acquired during a ten months curricular internship at Blueclinical – Investigação e Desenvolvimento em Saúde, Lda (hereinafter "Blueclinical"). The internship took place during the second year of the Master's Degree in Pharmaceutical Medicine at the University of Aveiro, beginning in July 2013 and ending in April 2014.

During my internship, my primary activity was the coordination of clinical research at a study centre – Hospital Centre of Vila Nova de Gaia/Espinho[1] (CHVNG/E). Clinical research coordination is a multidisciplinary job, where the contact with other people is crucial to accomplish tasks successfully. My core activity was developed in the context of Blueclinical Clinical Research Partnership (CRP), which is one of the Blueclinical's main functional areas. Besides CRP the other areas are Research & Development (R&D) and Phase I (PHI).

My internship can be split in two different phases, the first one between July 2013 and mid-January 2014, when I was based at CHVNG/E as Clinical Research Coordinator Trainee, and the second one between mid-January 2014 and April 2014. The second phase started when I left CHVNG/E and went to Hospital Centre of Tondela-Viseu (CHTV). Due to external factors I did not stay a long period at the hospital, so during the last few months of my curricular training I developed my activities at different study centres and also at the Blueclinical back office.

In this report I describe what I have done and the professional experience I have gained, regarding the context of the company activities and the clinical trials area. To allow this contextualization, the present chapter provides an overview of Blueclinical history and organization. After that, my training objectives are presented, both the ones related with the company and the general ones.

The remaining report will be organized as follow: 2. Clinical Research State of Art; 3. On the job training; 4. Discussion; 5. Conclusion.

[1] A Hospital Centre, according with the Portuguese national law is considered a collective person, with financial and administrative autonomy. It gathers together different and autonomous hospitals but their coordination and/or Administration is common (39).

Chapter 2 provides the state of art of clinical research, describing what clinical trials and observational studies are, the main differences between them and the applicable legislation. The changes that are occurring nowadays are also described.

In the third chapter, the activities I have performed CHVNG/E, Hospital Centre of Baixo Vouga (CHBV), CHTV, Hospital Centre of Cova da Beira (CHCB) and Blueclinical's back office are described.

In chapter 4, I discuss how the internship contributed to the improvement of my skills, what were the main challenges I have faced and how my academic background has influenced my daily job. Both the positive and negative issues of my internship are presented as well as the way I have faced them. Furthermore the achievement or failure to reach the objectives I have defined in subchapter 1.2 is debated.

The last chapter is a conclusion of the report where I sum up all the relevant issues of my curricular training, such as the experience acquired, major problems and successes.

1.1. BLUECLINICAL – INVESTIGAÇÃO E DESENVOLVIMENTO EM SAÚDE, LDA

Blueclinical – Investigação e Desenvolvimento em Saúde, Lda. (1) is a company created in 2012. Blueclinical's competences cover every single phase of the research and development of new drugs – from bench to bedside.

As previously referred, Blueclinical is organized in three main functional areas: R&D, PHI and CRP. The company logo (Figure 1) is a representation of those three areas, being each area represented by a different tone of blue.

Figure 1 – Blueclinical Logo. The three functional areas are represented on the rectangle above the company name. Reproduced from Blueclinical's website (1).

Blueclinical R&D provides support to institutions and companies in the different stages of the research and development of new products (drugs, medical devices and other health products) process (1,2). The mission of R&D is to empower translational research in Portugal, being a contribution to the transformation of basic research into new therapeutic and diagnostic products and services (2,3).

Blueclinical PHI is a centre to conceive, organize and develop phase I clinical trials, with different medicines (1). PHI headquarters are at Hospital da Prelada, Oporto, and have 29 beds available for clinical trials on healthy volunteers (phase I studies) or selected patients populations (early proof-of-concept studies) (4,5).

Figure 2 – Blueclinical CRP network, on April 2014. Logos of the institutions and of the offices created at each institution. Reproduced from Blueclinical's website (7).

Blueclinical CRP provides organizational support to clinical investigation on health care institutions (1). According to the company website, its mission is to "support the activity of

clinical research centres, promoting their growth, efficiency gain and achieving a reputation for excellence in clinical research" either promoted by pharmaceutical/medical devices industry or promoted by institutional investigators (6). At this moment, thirteen different institutions are gathered at CRP network (Figure 2). Belonging to the CRP network means that a clinical research office will be set up at the institution, counting with at least one Blueclinical collaborator at the office. The first office was created on CHCB in January 2013, followed by the office on CHVNG/E in April 2013. The newest centre of the network is placed at Hospital Centre of Trás-os-Montes e Alto Douro.

This network allows sharing the best practices in clinical investigation, the harmonization of procedures, and provides institutions enough size to be advertised outside Portugal. Blueclinical supports the qualification and European Certification of investigation teams (6).

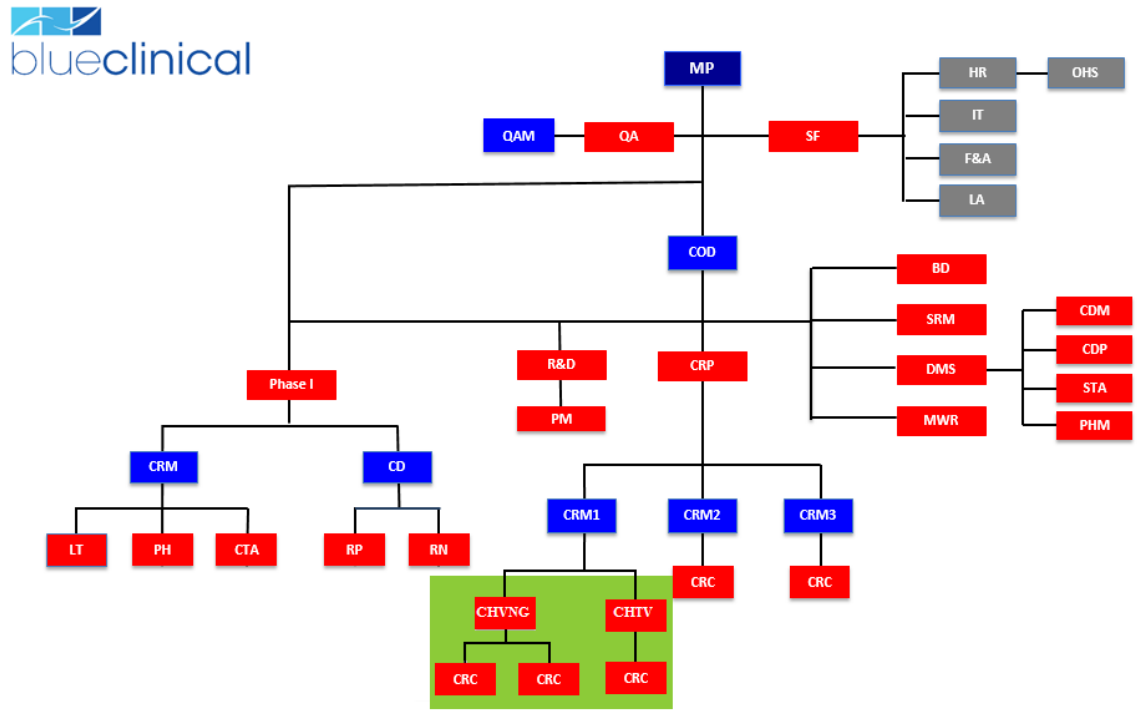


Figure 3 – Blueclinical Organogram. Areas where I developed my internship activities are highlighted in green. Adapted from Blueclinical's Quality Manual (8).
(*BD* – Business Development; *CD* – Clinical Director; *CDM* – Clinical Data Management; *CDP* – Clinical Data Programming; *COD* – Clinical Operations Director; *CRC* – Clinical Research Coordinator; *CRM* – Clinical Research Manager; *CRP* – Clinical Research Partnership; *CTA* – Clinical Trial Assistants; *DMS* – Data Management and Statistics; *F&A* – Finances and Accounting; *HR* – Human Resources; *IT* – Information Technology; *LA* – Legal Affairs; *LT* – Laboratory Technicians; *MP* – Managing Partners; *MWR* – Medical Writing and Reporting; *OHS* – Occupational Health and Safety; *PH* – Research Pharmacy; *PHM* – Pharmacometrics; *PM* – Project Management; *QA* – Quality Assurance; *QAM* – Quality Assurance Manager; *R&D* – Research and Development; *RN* – Research Nurses; *RP* – Research Physicians; *SF* – Support Functions; *SRM* – Safety Risk Management; *STA* – Statistics)

Nowadays Blueclinical counts with, approximately, forty-five internal collaborators, twenty-two of them allocated to CRP. The organization of Blueclinical is described in Figure 3.

During my training, I had closer contact with the two clinical research coordinators (CRC) of CHVNG/E, the Clinical Research Manager (CRM) of CHVNG/E, CHTV and Hospital Centre of Alto Ave and with the Clinical Operations Director (COD).

1.2. TRAINING OBJECTIVES

During the first year of my master degree I decided that I would do a curricular training. At the time, I established some objectives that I intended to achieve independently of the company where I was going to be. Those objectives are:

- Improve my communication skills, both written and spoken;
- Improve my autonomy, self-confidence, organization, team group working skills, sense of responsibility;
- Use the knowledge acquired both in my degree and master degree;
- Develop my professional network.

After knowing I was going to Blueclinical and after understanding the CRP objectives and mission, as well as my job role, I set the following objectives:

- Be acquainted with the steps and procedures to implement a Clinical Investigation Centre at an Hospital;
- Know how to plan, conduct and coordinate a clinical trial/observational study from feasibility to close-out visit, regarding the applicable legislation, patients and monitoring visits preparation, CRF (Case Report Form) filling, query resolution, etc.;
- Learn how to review and improve financial agreements;
- Learn how to create and maintain a quality system, as well as prepare the centre to inspections or audits;

- Create a relationship with physicians and other clinical trial personnel, in order to motivate themselves and to augment their compliance with GCP's (Good Clinical Practices);
- Develop a balanced relationship with Blueclinical's collaborators both to maintain a positive working environment and to help each other on daily activities;
- Contact with patients and try to make their participation on clinical trials easier;
- Contribute both for the development of Blueclinical and of other institutions where I have been based regarding Clinical investigation;
- Acquire basic knowledge in clinical trials monitoring tasks.

2. CLINICAL RESEARCH STATE OF ART

The main objective of this chapter is to provide the theoretical basis of this report, regarding what clinical research, clinical trials phases, and applicable legislation are. The chapter is divided in three sub chapters, the first one about clinical trials, the second one about observational studies and the third one about legislation.

2.1. CLINICAL TRIALS

According to the directive 2001/20/EC (9), clinical trials are “any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy” (9).

Traditionally the R&D model is described as a four sequential phases’ process, based on “trial and error". In practice, those phases are not sequential, as one type of trial could occur at different time points of the drug development process, or studies from different phases could take place at the same time. A classification system based on the studies objectives was developed (10). Each term of this classification system corresponds to one phase as described below:

- Phase I - or Human Pharmacology Studies. These studies are designed in order to assess tolerance, determine pharmacokinetic and pharmacodynamic profiles, describe the drug metabolism and interactions and identify the maximum tolerated dose. Usually these studies are performed on healthy volunteers (10).
- Phase II - or Therapeutic Exploratory Studies. These studies are developed on the target patient population with the intent of estimate the dosage for following Studies, and define the preliminary tolerability/safety profile in patients (10).
- Phase III - or Therapeutic Confirmatory Studies. These studies are performed on larger patient populations, being the selection criteria as similar as possible to the daily routine conditions. Their objective is to confirm the therapeutic effectiveness and set the conditions of usage in regular medical routine (10).

– Phase IV – or Therapeutic Use. These are usually post-marketing approval studies, designed to provide further information on the therapeutic effectiveness in real life conditions. They also assess the value of the new medicine compared with the existing alternatives (10).

This R&D model is becoming unsustainable for the pharmaceutical industry as it is very expensive and has very high failure rates (Figure 4 and Figure 5). The problems of this R&D model are:

– Too slow – easily a compound takes 15 years to be placed in market. Patents are 20 years long, so companies only have 5 years to achieve profits (11,12).
– Too expensive – the total cost of bringing a new drug to market could reach more than 1000 million US dollars, a value that largely increased in the past few years (11,12).
– High failure rates – in average for each drug that launches market, approximately 24 compounds have to initiate the preclinical phase. The lowest successful rates happen between phase 2 and phase 3, the most expensive phases (11,12).
– Too inefficient – in spite of the increase of costs, which means an increase in investments, the number of drugs that are placed in market is decreasing (11,12)

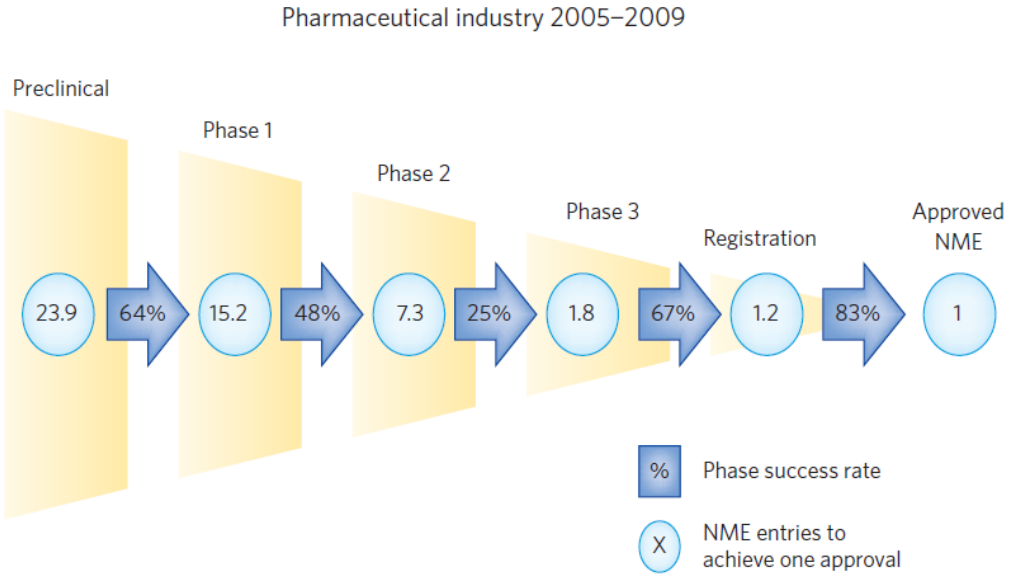


Figure 4 – New Medical Entities (NME) vs success rates. Data from the 14 large pharmaceutical companies' regarding the approval of one NME. Reproduced from 13.

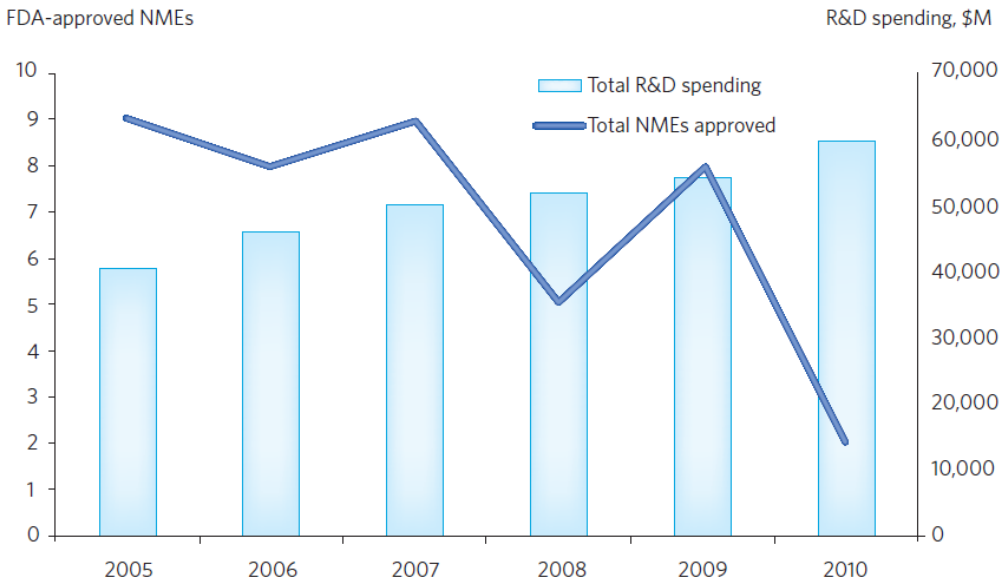


Figure 5 – Pharma productivity between 2005 and 2010. R&D costs versus NMEs approved, regarding 9 of the largest pharmaceutical companies. Reproduced from 13.

The traditional R&D model no longer answers the necessities of pharmaceutical industry. Looking for a change, two different programs were developed – IMI (Innovative Medicines Initiative) and CPI (Critical Path Initiative).

IMI is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients (14). CPI is United States Food and Drugs Administration's (U.S. FDA) national strategy for transforming the way U.S. FDA regulated medical products are developed, evaluated, and manufactured (15).

These two initiatives pointed out a new R&D strategy that is focused in the study of the pathophysiology allowing the development of better compounds, using better targets and new biomarkers (Figure 6).

The use of bioinformatics, adaptive trial designs, historical control data, together with better targets and new biomarkers, allows that the development of new compounds fail at an earlier point, before the expensive stages (phase II and III trials) (16).

The new R&D strategy is first of all based on a better knowledge of the pathophysiology and epidemiology of diseases. This knowledge will be achieved prior to the initiation of

the expensive development phases. It will be necessary to know the diseases subtypes and their nature and incidences; physiological mechanisms that could be the target of treatments; biomarkers that can differentiate patients groups, personalizing therapeutics (11).

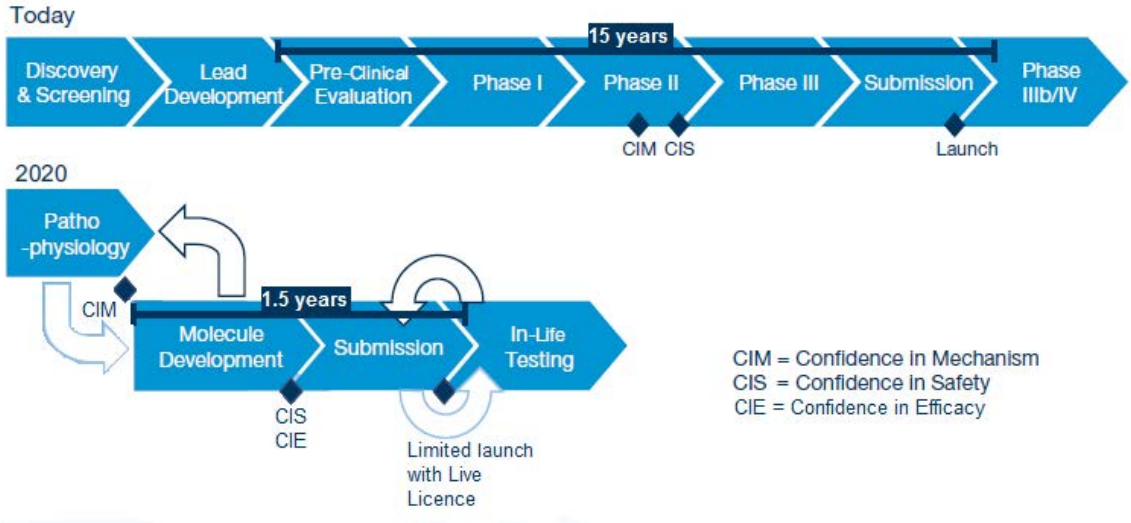


Figure 6 – The new R&D model. Comparison between the traditional and the new R&D models. Adapted from 11.

Only after there is confidence in mechanism, the R&D process will proceed to other step, which is the molecule development (Figure 6). This step regards the performance of highly targeted clinical studies, supported by simulation, modelling and other technologies. The objective is to achieve confidence in safety and in efficacy. When there is enough data to support the drug use in a certain target population, submission to the regulatory authorities can be made. This submission will be limited to that target population – limited launch (Figure 6). After obtaining the first launch authorization, the drug will enter a development loop to extend the marketing authorization to other populations or other indications – limited launch with live licence. This new approach will make the R&D process more efficient, effective and less expensive. Patients will be able to have access to new medicines at an earlier stage (11,12).

Earlier this year, the European Medicines Agency (EMA) launched an adaptive licencing pilot project whose objective is to faster the access of patients to new medicines. Companies who will take part of this project will have their medicines authorized at an earlier stage of the drug development although its marketing is restricted to controlled

patient populations. As further information is gathered, the marketing authorization could be updated, in order to expand the use of the medicinal product to larger groups of patients (17).

2.2. OBSERVATIONAL STUDIES

An observational study is a study that searches out data about people that *per* standard of care take a specific drug, or activity or lifestyle. It is also called non interventional study as no procedure is done outside the daily medical routine (18). Observational studies tend to be less complex compared with clinical trials.

Depending on the observational studies design, they can be classified as:

- Case-Control – study that starts with the effect (disease) and goes straight to the cause;
- Cohort – it is similar to a clinical trial because it starts with a cause and directs to the effect. The groups are formed by observation of exposure or no exposure on real life;
- Cross-Sectional – in these studies the cause and the effect are detected simultaneously (18).

Observational studies can be conducted at a point in time or be longitudinal ones. In longitudinal studies multiple measurements are performed during a period of time. It is possible to assess changes, as a unique group of population is studied (18).

These studies can also be prospective or retrospective. Retrospective studies use already archived data, for example by patient files research. Prospective studies are characterized by the enrolment of subjects in advance and following them through a defined period of time (18).

Observational studies usually are performed as post-market authorization studies, in order to collect additional information on safety and efficacy (18).

2.3. LEGISLATION

Clinical research is a highly legislated area. Looking backwards to the history of regulations, in 1848 the United States of America took the first regulatory action regarding drugs. The Drug Importation Act was created forbidding the import of adulterated drugs (19). The first attempt to legislate medicines and food happened in 1906 with the Pure Food and Drugs Act, created by President Roosevelt.

In 1947 the Nuremberg Code was established as a consequence of "The Nazi Doctors Trials" (19). Nuremberg Code was developed by four American judges involved in the judgement of the Nazis doctors. It is a ten-point document with the basic principles of ethical behaviour while conducting experiences in human. This code is still followed today.

The Declaration of Helsinki was established in 1964. Although it repeats the Nuremberg code requirements, it praises the use of written consent and defines as mandatory the prior review and approval of the protocol by an Institutional Review Board. Declaration of Helsinki is morally binding for physicians, and whenever its statements provide higher protection for subjects, the declaration overrides the national or local laws and regulations. Periodically this document is reviewed and new versions are published (19).

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was formed in 1990 in order to achieve a unified standard for the European Union (EU), Japan and United Stated, which allows the mutual acceptance of clinical data, by each party regulatory authorities (19). ICH provides guidelines concerning Institutional Review Boards and Institutional Ethics Committees; investigator; sponsor; protocol and protocol amendments; investigator brochure and other essential documents. Regarding clinical trials, ICH Good Clinical Practices (ICH-GCP) (20) are probably the most important guidelines. Some of the ICH-GCP principles are:

- Risks and benefits should be carefully assessed;
- The rights, safety and wellbeing of trial subjects are the most important;

- Trial should be supported on the available information about the investigational product;
- All medical care of and decisions about study subjects should be responsibility of a qualified physician;
- All subjects that enter a trial should provide their consent in a freely and informed manner;
- Good manufacture practices should be followed during the manufacture, handle and storage of the investigational product.

Later, the co-existence of ICH-GCP and country local legislation became a problem when implementing a multicentre clinical trial. EU, in 2001, published a directive on clinical trials (9) that was transposed to the state members' national law prior to 1st May 2004. The objective of the directive was the harmonization of laws, regulation and procedures through the Member States.

On 2005 a new directive (21) with principles and detailed guidelines for good clinical practice was launched. It regards not only the investigational medicinal products for human use, but also the requirements for authorization of the manufacturing or importation of the investigational products.

Due to the increase of the costs associated with the conduction of clinical trials and the decrease in new clinical trials, EU Members States considered that it was necessary to act, so they presented a proposal for a regulation (22). This year, the Regulation (23) was approved by the European Parliament and by the Council.

Comparing the new regulation with the 2001 (9) and 2005 (21) directives, several changes could be noticed. The first main alteration is that the new regulation has legal force throughout every Member State, without need of national implementation (9,23).

Alterations to the authorization procedure have been done. The entire procedure is now regulated in a more detailed way. The procedure can be summarized as follows: submission of an application dossier to the chosen Member States, proposing the reporting one; the reporting Member State has 6 days to inform the sponsor about: 1) whether they accept or not being the reporting Member State, 2) whether the clinical trial fulfil or not the

scope of the regulation, 3) whether the application is complete or not and 4) whether the clinical trial is or not a low intervention clinical trial (only when requested by the sponsor). When reporting member gives no information to the sponsor, all the previous items are applied. If information is incomplete or any other problem is noticed, the sponsor has 6 days to comment and/or complete the application. If sponsor does not provide an answer within those 6 days, the authorization procedure is withdrawn. If there is no notification by the reporting Member State within 3 days after the submission of sponsor's answer, the application should be considered complete. All the communications labelled before will be performed through EU portal (23).

Chapter 3 substitutes article 10(a) from directive 2001/20/EC, on the explanation of the authorisation procedure for a substantial modification of a clinical trial. This explanation is made in much more detail than before. Information provided in chapter 4 has no equivalent information in the directive. Jointly with annex 1, this chapter defines rules on the content of the application dossier.

Chapter 7 is about safety reporting. The report of adverse events (AE) follows the practice set up in directive 2001/20/EC. The report of serious adverse events (SAE) follows the same practice, being reported to the sponsor. Only the unexpected serious adverse reactions are reported to the EMA, by an electronic database set up and maintained by the Agency. The Database must include the safety reports. The sponsor must report without delay the unexpected SAE occurred in its clinical trial. The timeframe of the report is determined by the severity of the reaction, and it could be submitted an incomplete report, followed by a complete report as soon as possible. If there is no possibility of electronic report, the event should be reported to the Member State, where the event happened. The Member State has the obligation of doing the electronic report. Besides these, this chapter defines rules about annual reporting to Member States and to marketing authorization holder, and assessment by Member States (23).

Directive 2001/20/EC (9) determines that all clinical trials must have an obligatory insurance/indemnity (9). In Chapter 12 the regulation (23) modifies this situation, setting that the insurance/indemnity is dependent of the risk of participating in the trial in comparison to the risk induced by normal clinical practice treatment (23).

Unlike in the directive, several annexes are present in the regulation. They contain more detailed information on some aspects defined in the regulation, such as the content of the application dossier and the safety reporting.

Although the new Regulation has already been publicized in the *Official Journal of the European Union,* it will be applied no earlier than the 28th May 2016 (23).

Regarding the Portuguese regulatory framework, two law-decrees were published on 1994 (24) and 1995 (25). Those were the first Portuguese laws on clinical trials. The Directive 2001/20/EC (9) was transposed to the law 46/2004 (26). This law established the obligation of favourable opinion from the Portuguese ethics committee – (Comissão de Ética para a Investigação Clínica - CEIC) and authorization from the Portuguese regulatory authority (Autoridade Nacional do Medicamento e Produtos de Saude, I.P. – INFARMED) and from Portuguese data protection commission (Comissão Nacional de Protecção de Dados).

The Directive 2005/28/EC (21) was transposed to the law-decree 102/2007 (27). Besides the information about good clinical practices, it has information on essential documents archiving and on inspections.

Personal data protection is regulated by law 67/98 (28), being the deliberation 333/2007 (29) exclusively about protection of personal data on clinical trials and the deliberation 227/2007 (30) about personal data protection on non-interventional studies.

The regulatory framework in Portugal is presently suffering a change, as the new law on clinical research (31) was approved on the 3rd April 2014, and will enter into force during June 2014. This new law revokes the law 46/2004 (26).

This new law not only regards the authorization and conduction of clinical trials but also their divulgation. The CEIC role is clarified as well as more responsibilities are assigned to the local ethics committee. It creates a national registry of clinical research (Registo Nacional de Investigação Clínica). The objective of the national registry is the increase of the interaction between all clinical research stakeholders (32).

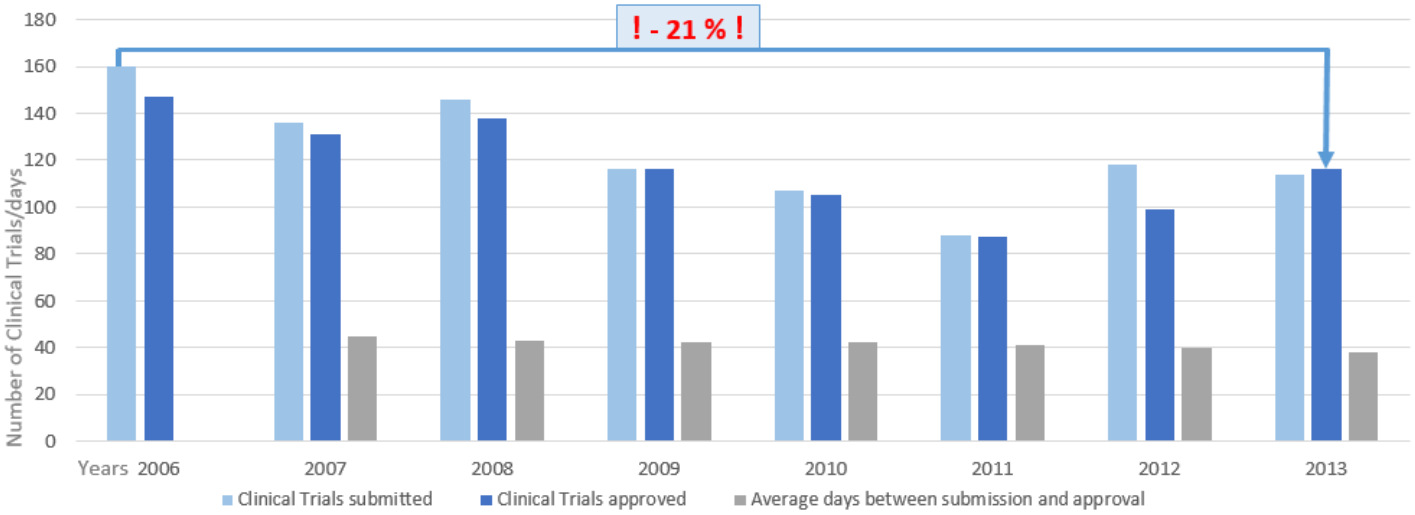


Figure 7 – Clinical trials in Portugal between 2006 and 2013. Approval times, number of submissions to INFARMED and approvals from the national authority. Between 2006 and 2013 the number of approved clinical trials decreased approximately 21%. Adapted from INFARMED (33).

The new law is seen as an opportunity to change the present situation of clinical trial. Since 2006 there is a considerable decrease in the number of clinical trials submitted to the Portuguese regulatory authorities (Figure 7). In 2011 just 88 studies were approved (33). Only if Portugal becomes more competitive and attractive to the pharmaceutical companies this situation could be changed (34).

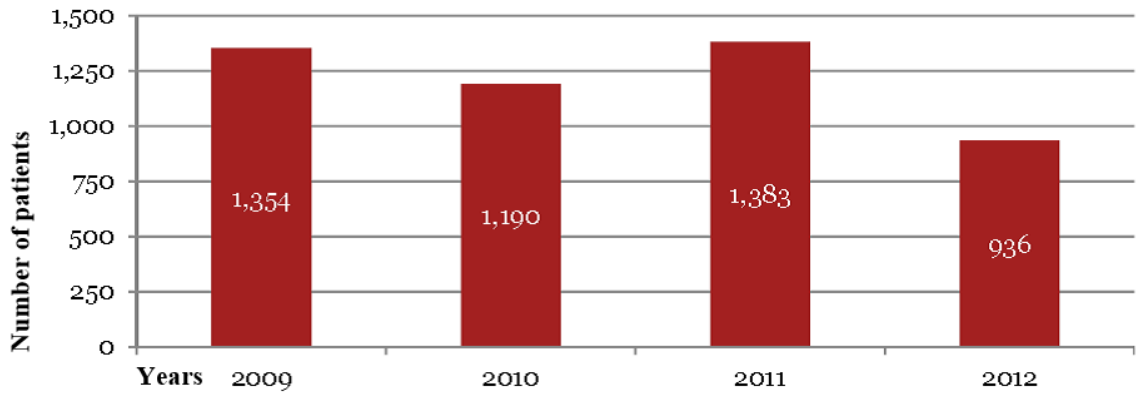


Figure 8 – Number of new patients recruited, in Portugal, *per* year, between 2009 and 2012. Excepting in 2011, the number of recruited patients has been diminishing. Reproduced from 35.

Patients' recruitment is a critical issue, as between 2007 and 2011 only 70% of the initial number of planned patients were enrolled (34). The low patient recruitment (Figure 8) could be a consequence of the reduced number of centers *per* study in our country, and also a consequence of the low recruitment capacity of each site (34).

The negative scenario of clinical trials do not only affect the reputation of Portuguese sites near the pharmaceutical industry, but also cause a negative impact on the financial system. In the pharmaceutical sector, every euro that is invested results in 1,98 euros, so creating competitive conditions to the conduction of clinical trials should be imperative (34).

3. ON THE JOB TRAINING

My collaboration with Blueclinical started on April 2013, when I had an interview with Cristina Lopes, the COD, and I was accepted to do my curricular internship there, as CRC. On 8th May 2013, I attended a training session where I met other Blueclinical's collaborators. Nevertheless my internship started on the 3rd July 2013. Since that day, until mid-January 2014 I was a full time study coordinator at CHVNG/E.

By the end of 2013 Blueclinical's administration board proposed me to move to Viseu to coordinate the local clinical research office. The CRP team was suffering changes in order to maximize the efficiency of the staff and fulfil the necessities of every hospital. As I have accepted the challenge, I had two weeks to finish my job at CHVNG/E and then two weeks to observe a different work strategy at CHBV. After that, I had to be ready to start working at CHTV in the first week of February 2014. As the administration board of the hospital raised issues about the collaboration with Blueclinical, I only spent there one month. The month of March was spent working home based at Viseu. During that month, I went to CHCB a few days to work there. In the beginning of April I definitively left Viseu and moved to the Blueclinical's back office (Figure 9).

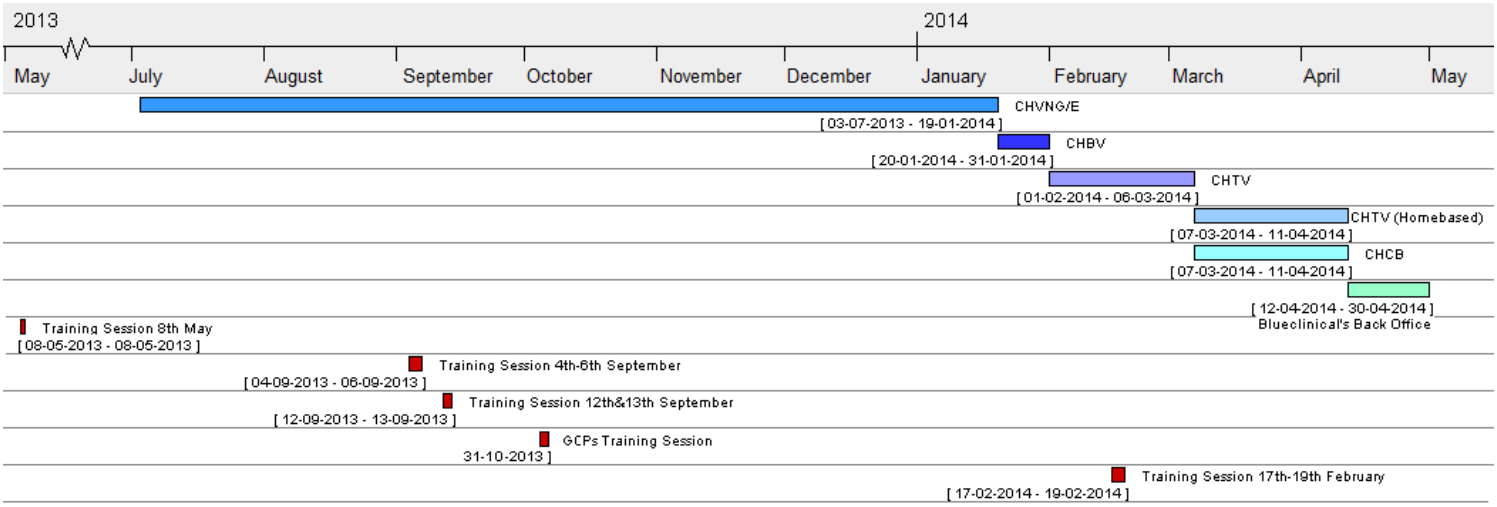


Figure 9 – Chronology of my internship – The hospitals where I was based are displayed as well as the training sessions.

In order to facilitate the description of the activities performed, this chapter is organized as follows: 3.1. – CHVNG/E; 3.2. – Other Activities Developed; 3.3. – Training. The first subchapter is divided according with the tasks I have done at CHVNG/E. Subchapter 3.2

describes all the activities performed at CHBV, CHTV, CHCB and at back office. The last subchapter contains a description of the training sessions I attended, both provided by Blueclinical and by external entities.

3.1. HOSPITAL CENTRE OF VILA NOVA DE GAIA/ESPINHO

CHVNG/E was created by the law-decree 50-A/2007, of 28th February 2007, gathering together Hospital Centre of Vila Nova de Gaia and the Hospital Nossa Senhora da Ajuda, from Espinho (35). CHVNG/E is divided into three units, being unit 1 in Monte da Virgem, unit 2 in the centre of Vila Nova de Gaia city and unit 3 in the centre of Espinho city.

Assuring high quality and efficient health care services is part of the hospital mission, as well as having highly motivated and satisfied professionals. The administration board also defined training, investigation and scientific development as part of the hospital mission (36). It is estimated that the population under the hospital area is about 700 thousands inhabitants (37).

Resulting of a collaboration agreement between Blueclinical and CHVNG/E, the Clinical Research Office (*Gabinete de Investigação Clínica* – GIC) was created with the objective of supporting clinical research from industry and from local investigators. The agreement was signed on 1st April 2013, and the first Blueclinical collaborator at the hospital started working on 16th April 2013. However, only a few months later, in July 2013, the physical installations were available.

GIC organizational structure is divided into three parts: coordination, Supporting Office to Clinical Research Office (*Gabinete de Apoio ao Gabinete de Investigação Clínica* (GAGIC)) and associate clinical investigators (Figure 10). GIC's coordinator is Doctor Hugo Tavares, a paediatrician at CHVNG/E unit 2 and one of the external experts nominated by INFARMED at the Paediatric Committee of the EMA. GAGIC is formed by Blueclinical's collaborators based at CHVNG/E. During my training, Sónia Correia was the Clinical Research Manager and myself, Daniela Cabeleira and Rita Espanhol (since September 2013) were the CRCs. Associated clinical investigators are the medical staff that desire to associate themselves with GIC and perform, successfully, the PharmaTrain

Clinical Investigator Certification, a training provided by Blueclinical. It regards training in clinical research, GCPs and clinical investigation quality system.

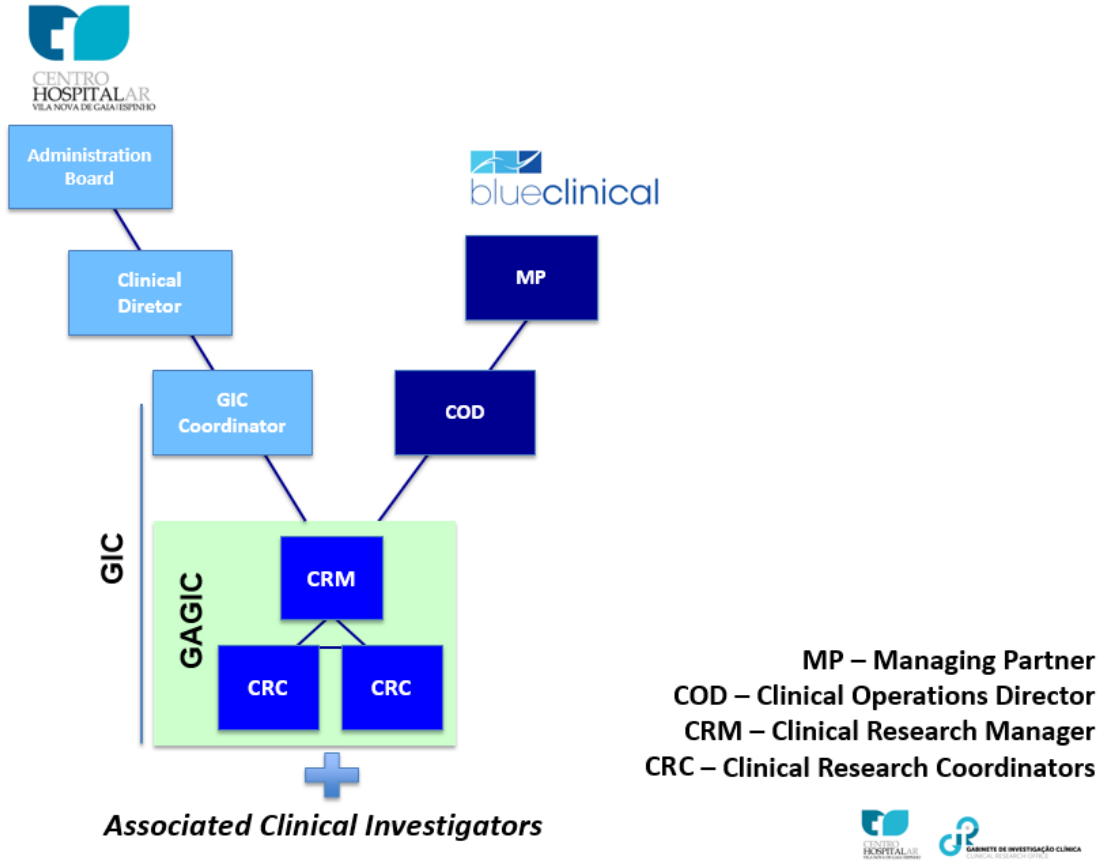


Figure 10 – GIC organizational structure. Adapted from Blueclinical and CHVNG/E collaboration agreement (38).

As my training started right after GIC creation, I performed several activities related with GIC implementation and its divulgation near the medical staff.

One of those activities was the presentation meeting to all the medical directors of the hospital that took place on 10th July. At this meeting, Blueclinical was represented by its Managing Partners Doctor Luis Almeida and Doctor Sergio Simões, the COD Cristina Lopes, and some colleagues based at other hospitals from the network. The CHVNG/E administration board president made an introductory speech, focusing the reasons why the hospital needed a Clinical Research Office. Doctor Luis Almeida, as the Blueclinical owner, also made a speech, presenting the current situation of clinical research in Portugal and explaining why the present scarcity of clinical trials could and should be seen as an opportunity to do more and to do better. The Hospital Clinical Director made his

communication referring how Blueclinical's projects matches the hospital strategic plan. He clarified that the main objectives of the partnership were achieving conditions to maximize clinical research at the hospital and contributing to the development of medical sciences. Afterwards, the GIC coordinator made a brief presentation of the GIC structure, competences, and the following steps to be performed by the office staff.

After this meeting, and by GIC coordinator initiative, a sequence of meetings with every clinical and non-clinical services took place. Those meetings intended not only to introduce GIC to CHVNG/E professionals on a more personal way but also to learn about the history of clinical research at the hospital and to know what are the expectations of the hospital staff regarding GIC collaboration.

An effort was made to provide suitable material to the office, such as computers, mobile phone, printer and more chairs and desks. For electronic material, written requests addressed to administration board were made, while chairs and secretaries were rescued from the old material repository.

The activities of GIC implementation and divulgation were a small part of the activities I have developed. All the activities I have performed were done in close collaboration with my office colleagues. I had the opportunity to participate in the following tasks:

- Templates development;
- Feasibilities
- Investigators meeting
- Initiation meetings
- Patients recruitment
- Patients visits
- Monitoring visits
- Other administrative tasks

During the time I spent at CHVNG/E, I coordinated three clinical trials on lung cancer, one clinical trial on diabetes and one observational study on psoriasis. On the lung cancer trials, I was involved on the randomization of two patients, following a total of 5 patients, and I

had one screening failure. On the diabetes clinical trial I followed 4 patients, and on the psoriasis study I was involved on the inclusion of one patient.

3.1.1. Templates development

The idea when creating templates is providing tools that help our work as well as harmonize the documents used. As GIC was recently created, there were only a few templates. Templates development is an ongoing task, as only with the use of the documents it is possible to evaluate their usability and utility. Frequently it is necessary to develop new ones or update the existing ones. There are templates for external use such as Curricula Vitae (CV), verification list for clinical trials and clinical/observational studies, submission letter and templates for internal use as tables for kits control, tables for listing concomitant medication and SAEs and AEs, tables to control participants expenses, tables to calculate exams or visits date, internal mail protocol, calendars, financial evaluation summary.

I have adapted the Blueclinical's CV template, adding the hospital and the GIC logos to the document, and indicating the hospital address. Besides the personal information, this CV requests information related with clinical research experience and relevant training courses, as these topics have major importance to sponsors. The template is supposed to be used by everyone that is part of GIC. Its divulgation was done by e-mail, requesting the receiver to fill in the document, print, sign and sent it back to the office. Under special circumstances, for example when there is a lack on language skills (the template is written in English), the template is filled in by GAGIC. I created a dossier with all CVs signed and dated, as well as a digital archive.

I have created verification lists for clinical trials and clinical/observational studies, submission letters, site facilities declaration templates using the documents previously developed at CHCB as a basis. These documents are an attempt to harmonize the submission dossiers at Blueclinical's network, and ease the work both from sponsors and Blueclinical staff. Verification lists summarize all the documentation necessary in the administration board submission dossier, and some specifications about them: mandatory content, availability of a hospital template, preferable language. Submission letters is one of the mandatory documents and it is supposed to be copied to the sponsor letterhead

paper. Its content includes a sum up of the project so that the administration board easily highlight the main aspects about the project. The site facilities declaration is a document completed by GAGIC in collaboration with the sponsor, regarding information about the conditions of the hospital facilities and the hospital staff available to perform the study. It is a statement about all the necessary facilities, equipment and staff, indicating whether it is provided by the hospital or by the sponsor.

Using a Microsoft Excel® workbook, I developed a controlling tool to keep the stock of kits for blood samples collection controlled. The tool created has automatic forms in a way that the number of available kits and the next expiration date are highlighted. The necessity of such tool results of the fact that visit kits could be a critical issue when coordinating a clinical trial, as different visits mean different kits, and each kit means an expiration date. This document needs periodic updates, either when kits are used, or destroyed and when new kits are delivered at the centre. For each new trial an update to the document has to be done, creating a new page to that trial, and identifying each kit's name.

Another document I have created was the template to control patients' expenses. Ethically, clinical trials' participants cannot have expenses due to clinical trial's procedures. Sponsors have the obligation of reimburse participants. On this document, besides information on the type, date and value of the expense, it is necessary the name of the study coordinator who received the expenses, the date when they are delivered to the clinical research associate (CRA), the CRA's name, and the date when participant receives the money, and his/her signature.

As GIC is part of the hospital structure, almost every day there is mail to be sent elsewhere inside the hospital. To keep a record of the sent mail and the date when it reaches its receiver, I have an internal mail protocol containing a sum up of what is being sent, the receiving date, and receiver's signature. It is part of each letter/dossier/package sent, and must be returned to the office by the receiver.

I have adapted the existent financial evaluation summary in order to make it easier to read. The objective of this document is to sum up the financial issues of a protocol and to ease the assessment performed by the administration board. This document contains information on study/trial name, sponsor, principal investigator (PI), beginning and ending

date, number of patients, value *per* patient and total estimated value, percentage of the total value for the involved staff, for GAGIC and for the hospital as well as the corresponding value.

3.1.2. Feasibilities

Feasibilities are questionnaires developed by sponsors to assess the potential of hospitals to develop a new protocol. Usually sponsors choose the investigators who they think are the most suitable to perform that protocol. When the sponsor does not have a specific investigator, the service director chooses one person of his/her medical staff to answer the questionnaire. Although there is not a model used to make the questionnaires, the majority of the approached topics are the same in every questionnaire. Usually feasibilities have questions about PI interests and experience, size and experience of the clinical staff, including study coordinators, characterization of the patients' population and of the hospital facilities.

During my stay at CHVNG/E, GAGIC coordinated the answer to 16 questionnaires from various sponsors. These contacts resulted in six clinical trials to be submitted or already submitted to administration board, eight clinical trials still waiting feedback from sponsor. Two of the clinical trials were cancelled. The target of these questionnaires were several clinical services as: haematology, pneumology, oncologic pneumology, rheumatology, paediatrics, gastroenterology, ophthalmology, neurology, nephrology and internal medicine.

From the 16 questionnaires answered by GAGIC, I had the opportunity to answer one of them with a neurology physician. Before contacting the physician I made a selection of questions. Questions related with specific services from the hospital, as for example the pharmacy, were sent to that service, so the answers were the most accurate possible. Then I scheduled a meeting with the physician, where she answered questions about her team, experience and patient population. After that, I collected the answers of all services and submitted the questionnaire online.

Some sponsors, after the submission of the feasibility, perform a qualification visit, to assess *in loco* the hospital facilities. I was present at one qualification visit in the

nephrology service. The visit began with the CRA explaining the protocol. After that the PI showed the facilities available to perform the trial. Issues like the possibility of performing the imaging exams requested by the protocol were discussed. Some documents, such as the Investigators Brochure acknowledge receipt, were signed.

3.1.3. Investigators meeting

I attended one Investigators' meeting. This meeting occurred in Coimbra and counted with sponsor's representatives and physicians from several hospitals where the clinical trial was going to begin soon. I was there as a CRC. The topics presented were: ICH-GCP; study drug pharmacological profile and clinical development; study protocol; Interactive Web Response System (IWRS); electronic case report form (e-CRF); AE and SAE reporting; tools for patients and investigators specific of the trial. Some issues such as ICH-GCP were briefly presented, and issues as the study protocol were presented in more detail causing discussion between sponsor and physicians, regarding the study procedures.

3.1.4. Initiation meetings

Initiation visits are the last step before the beginning of recruitment at a site. These visits are usually made by the CRA responsible for monitoring the clinical trial at the site. Ideally every team member should be present, so it is made an effort to schedule a time suitable for the majority of the staff. Normally, when this visit occurs, the study material is already at the site, as well as the study medication.

This visit has two main objectives: giving training on the protocol to all the study staff and complete the delegation log. The delegation log is a document where everyone that takes part of the clinical trial staff is listed and their responsibilities are assigned. It also includes the date when the person becomes part of the staff and the date of exit, if it occurs prior to study termination. The PI must confirm the entrance and/or exit of every staff member, by dating and signing the log.

I was present at three initiation visits, one at the dermatology service, one at the pneumology service and one at the immunoallergology service. At the dermatology meeting only the PI and the sub investigators were present, as this meeting regarded an

observational study. At the other meetings, besides the PI and sub investigators, nurses and a pharmacist were also present.

During these visits everyone received training on the protocol, credentials and explanations on IWRS and e-CRF systems, and the objectives of the clinical trials and inclusion/exclusion criteria were reviewed. Predicted timelines for milestones, such as half of the study population enrolled or end of enrolment were presented. At the dermatology meeting, as the service had little experience working with study coordinators, I explained which activities can be performed by the study coordinator, as for example fill in the CRF. During the visit, the medical staff identified the first patient to be included in the observational study.

3.1.5. Patients recruitment

The financial agreement signed between the sponsor and the hospital for every clinical trial or observational study establishes the number of patients to include in each study. For some studies it is possible to pre-screen patients, reviewing patients' files, or patients' databases, and when the enrolment period starts patients are included in the trial. This works for chronic diseases, like diabetes or chronic obstructive pulmonary disease. For diseases with faster development, like cancer, or for acute diseases, it is not possible to predict when there will be a patient to be enrolled. For these trials enrolment strategies have to be different. As I coordinated trials on lung cancer, the strategies I followed were attending at the weekly group meeting, distribute summary cards between the physicians and sometimes consult a database. During the group meetings physicians discuss the therapeutic alternatives for patients who were newly diagnosed with lung cancer or who had recently relapsed. My job was to evaluate if any of those patients fit the main inclusion criteria of the studies with open enrolment, or when physicians had doubts about the studies clarify them. Frequently it was hard to understand what physicians were saying, due to the specific terms used. I had the necessity to establish some key words that I can easily identify. If I heard one of those key words I had to find out if the patient being discussed fitted the inclusion criteria.

I have done summary cards with the main specifications of the y, like, target disease, therapeutic line, experimental and reference drugs, and main inclusion criteria. The cards

were pocket size, so they fit the physicians' lab coat pocket, and physicians can always be aware of the trials with open enrolment. For one or two times I had looked at the database with lung cancer patients, attempting to identify patients who could relapse and have criteria to enter the study. The search was done considering the diseases subtypes and the stages.

Every time a patient was identified to enter a study, namely at the group meetings, I had to prepare the next consultation, moment when the physician presented the study and the informed consent form to the patient. For that visit I prepared a file with a checklist with all the procedures that have to be performed, the informed consent, a list of the inclusion/exclusion criteria, requisitions for imaging exams and a schedule for the next visits and treatments, if applicable.

For the psoriasis study the patient was identified by the investigators team, who informed me during the initiation visit. When the patient visit was scheduled I was notified to prepare the necessary documents.

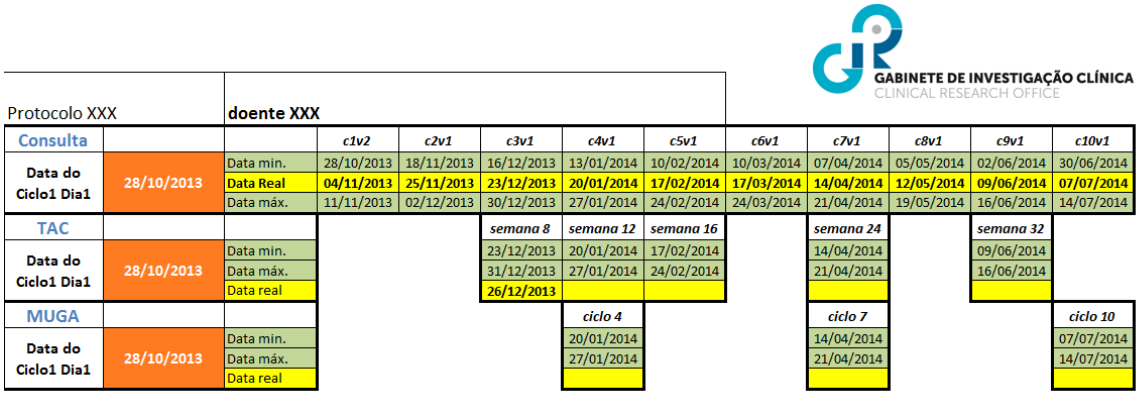
3.1.6. Patients visits

Before patient visits I performed several activities with the objective of simplify the visit, both on my perspective and the physician perspective. So, I prepared a worksheet that summarises the information that must be registered on the patient file, and identify important information that has to be followed up, like AEs and concomitant medication.

To manage concomitant medication I used a worksheet where I registered every new medication and every update to the current medication, according with the information requested on the protocol. This worksheet depends on each protocol specification, but usually regards the medicine name, dosage, onset and offset date and therapeutic indication. I used a similar worksheet to manage AEs, requesting information like starting and ending date, relationship with study drug and grade. While preparing the next visit I checked on these worksheets the ongoing medication and AEs, and then made annotations on the physician worksheet so that he or she update the information.

Another thing necessary to do is scheduling the following visits and imaging exams. These schedules were made according to the protocol and using a document with automatic fields

that calculates the time frame for the visit or exam and the preferable date (Figure 11). In this document in accordance with the protocol I previously defined the timeframes for each treatment cycle and for each exam. When a patient was randomized I entered the randomization date in the appropriate cell and then automatically all the timeframes were displayed. Imaging exams were made at an external facility, so I did a phone call in order to schedule the exam and then sent the requisition by e-mail. I also wrote down the next important dates and gave them to the patient during the visit.



GABINETE DE INVESTIGAÇÃO CLÍNICA
CLINICAL RESEARCH OFFICE

Protocolo XXX		doente XXX										
Consulta			c1v2	c2v1	c3v1	c4v1	c5v1	c6v1	c7v1	c8v1	c9v1	c10v1
Data do Ciclo1 Dia1	28/10/2013	Data min.	28/10/2013	18/11/2013	16/12/2013	13/01/2014	10/02/2014	10/03/2014	07/04/2014	05/05/2014	02/06/2014	30/06/2014
		Data Real	04/11/2013	25/11/2013	23/12/2013	20/01/2014	17/02/2014	17/03/2014	14/04/2014	12/05/2014	09/06/2014	07/07/2014
		Data máx.	11/11/2013	02/12/2013	30/12/2013	27/01/2014	24/02/2014	24/03/2014	21/04/2014	19/05/2014	16/06/2014	14/07/2014
TAC					semana 8	semana 12	semana 16		semana 24		semana 32	
Data do Ciclo1 Dia1	28/10/2013	Data min.			23/12/2013	20/01/2014	17/02/2014		14/04/2014		09/06/2014	
		Data máx.			31/12/2013	27/01/2014	24/02/2014		21/04/2014		16/06/2014	
		Data real			26/12/2013							
MUGA						ciclo 4			ciclo 7			ciclo 10
Data do Ciclo1 Dia1	28/10/2013	Data min.				20/01/2014			14/04/2014			07/07/2014
		Data máx.				27/01/2014			21/04/2014			14/07/2014
		Data real										

Figure 11 – Exams and visits schedule tool. When entering the date of cycle 1 day 1 (randomization), every other date is displayed.

On the day before the protocol visit, I left the physician worksheet and the medication prescription on the patient file. I also checked, near the nursing team, if the blood sample kit was prepared and if there was a questionnaire available to be given to the patient.

On the visit day I attended the patient consultation, so I could help the physicians with any issues they had, mainly during the first visits or when the patients relapsed. After the physician evaluated the patient and decided that he/she was going to continue on the trial, I did the IWRS call. During this call a new medication kit was assigned to the patient. After that, I went to the pharmacy to pick up the medication and then I delivered it to the patient. Before or after the consultation, I tried to talk with patients, in order to know how they felt, give them the expenses money and receive the new expenses tickets. I also tried to ensure that they knew when the next appointment was and that they did not forget the dates. I also tried to make sure they did not forget to keep the medication packages and bring them on the follow visit.

After the visit, on the same day, or on the following day, I had to fill in the CRF. Basically what I had to do was transcribing the information on the patient file to the sponsor e-CRF.

It was usual that during the visit, physicians forgot to write some details, as medication dosages, or AEs grades, that was mandatory information to full fill the e-CRF. So, on a post-it, I noted down the missing information and left it on the patient file. As soon as I had the opportunity, I contacted the physician in order to solve the pending issues. Although filling the e-CRF was a relatively simple task it took a considerable period of time. First of all, sometimes the necessary information was not completely available on the visit registries, mainly in the first visits, when demographic data and medical history was collected. So it was necessary to consult previous medical registries in order to find that information, and as a last resource contact the physician. Then, there were the e-CRF queries. There were three types of queries: automatic queries, data managers' queries and CRAs' queries. Automatic queries rised right after the introduction of data on the e-CRF. Usually regarded introduction errors (a comma used instead of a point, for example) or non-conformant data (for example, body temperature outside the frame defined *per* protocol). Normally these queries were easy to solve as it was only necessary to correct the wrong data or to confirm that the data available is correct. Data manager's queries were usually more specific, as they were related with protocol procedures or safety data. These queries usually took longer to be solved as it was necessary to talk with the physicians to clarify them. CRA's queries normally were raised after monitoring visits. They were about data not in accordance with the medical registries or missing data.

Every time patients gave me their expenses, I copied them and send them by e-mail to the sponsor, in order to speed up the payment to the patient, which easily took longer than a month. When the sponsor's representative gave me the money I gave it to the patient, as soon as possible. If the patient had left the trial, I called them, or any relative, if the patient died meanwhile, asking them to go to the site to receive the money. New strategies to simplify this procedure were discussed between GIC, sponsors and the hospital, being the transportation to the hospital provided by the sponsor one of the possibilities analysed. Some studies started to use this method.

SAEs had to be reported to sponsor on the 24 hours after any element of the team acknowledge the event. The way SAE were reported depends on sponsors. Sometimes a SAE form was sent by fax and sometimes they were directly reported on the e-CRF. The initial report usually had few information, so it was mandatory to do follow-ups. After

acknowledge the occurrence of a SAE and after identifying the way the report was done, I contacted the physician to fulfil the SAE form. After that, I submitted the form. In this initial report the information provided usually was the diagnostic, the initial therapeutic performed, the onset date and if there was any relation with the experimental drug. On the following days, I checked the patient file to get up-to-date information on the patient status and contacted directly the physician. When necessary, a follow up to the SAE was performed, updating the medication, laboratorial results and the outcome of the event.

For observational studies no procedures outside the normal practice could be performed. So the checklists I developed were only used as a guidance to ask the physician if any of that information was available. After the visit I only had to fill in the e-CRF and if there was missing information I had to state on the e-CRF that these information was unknown.

3.1.7. Monitoring visits

Monitoring visits were a responsibility of the sponsor. During this visit, CRA performed source data verification, and checked the trial master file, for example. I had some tasks during these visits. I had to schedule the monitoring visits, regarding the PI and the CRA availability. I also had to make sure that the CRA had the necessary conditions to perform the visit – facilities, up-to-date e-CRF, and source data documentation available. Then, I had to correct all the mistakes identified by the CRA, for example correct a value wrongly entered on the e-CRF. When the issues identified had to be corrected in collaboration with the investigators, I must solve the issues with them at their earliest convenience.

3.1.8. Other administrative tasks

The trial master file (TMF) was a dossier with important documentation of the trial. It had to be kept up-to-date, and this is a responsibility of the site staff. The delegation log was part of the TMF documentation and was a document where all the site staff was listed and their responsibilities were assigned. For the trials I coordinated I was responsible to maintain this document, so every time someone left the team, he or she had to register the date they left and sign. After that the document had to be signed by the PI. Other document present at the TMF was the Investigator Brochure and the protocol. When a new brochure or protocol was released I had to archive it and give the medical staff a document

where they stated that they have received the new version. The informed consent form was another document that could have new versions during the trial. In this case, I had to assure that every patient signed the new version of the informed consent form as soon as possible. Physicians had to explain the main changes on the informed consent, and the patients signed it if he or she wants to keep on the trial. The signature of the new informed consent form had to be documented on the patient file. One blank informed consent form had to be archived on the TMF and the old versions marked as outdated.

Another responsibility I had at GAGIC was the payments control. On one hand, I maintained a document for each ongoing study, where all visits were registered as well as the value of each visit. On the other hand, I kept a document controlling the payments performed to the hospital, with the indication of the amount correspondent to GAGIC. The periodicity of payments was defined on the financial agreement between the hospital and the sponsor. When the sponsor pretended to pay to the hospital, the financial department was contacted in order to issue an invoice. After receiving the invoice, the sponsor performed the payment. It was internally defined that when the financial department received an invoice request, GAGIC was contacted by e-mail to inform if the values were correct. To check the values listed by the sponsor, I compared the sponsor request with the document where I controlled visits. Usually all the values were correct so I just had to inform the financial department of the division of the amount received. That amount was usually divided between the hospital, GAGIC and the clinical staff.

As I had already stated, I created a document to control kits for blood samples stock. Using this document, at least once a month, I checked the stock and updated the document. If there were kits that had reached the expiration date, I destroyed them, saving the material that had no expiration date. If there was a small number of some type of kits, and I knew they would be needed soon, I requested them to the central lab, usually sending a request form with the amount of kits needed, by e-mail or by fax.

As I was part of Blueclinical, I had some tasks that were a specific request of Blueclinical. The agreement between Blueclinical and the hospital established that a trimestral report had to be sent to the administration board. I developed that report twice. It was a sum up of all activities developed during the previous three months. The main objective of this report was letting the hospital administration board know which activities we had developed, and

if the clinical research at the hospital was increasing or decreasing. Another task was the development of a database with all feasibilities answered, including the sponsor feedback, and all ongoing clinical trials, including information on number of recruited patients and value *per* patient.

3.2. OTHER ACTIVITIES DEVELOPED

As I said before, I left CHVNG/E in mid-January, and since then I spent some time at CHBV, CHTV and CHCB. At all the hospitals the activities performed by the CRC were more or less the same, so I kept on doing what I had learned at CHVNG/E, implementing some adaptations due to each hospital characteristics.

At CHBV I was not responsible for any task as I spent little time there. I just followed the local CRC during her daily activities. I had the chance to learn how biological samples were processed, and sent to the central laboratory. I never had to process the biological samples, as at CHVNG/E it was a responsibility of the nursing team or of the local laboratory. Unlikely what I thought, the processing itself was a simple task as the laboratorial manual explained all the steps. After centrifugation, samples were placed on proper packing, so they could be sent to the central laboratory.

During the days I spent at CHBV, I was alerted to some practices that are preferable to implement when the clinical research office only had one person. It was the case of preparing kits in advance, for example, at the end of one week prepare all the kits for the following week. A little more time could be wasted on that day, but while the patient was at the site, it was one less thing to do.

At CHTV I had some new experiences. First of all, I had to make great pressure near the hospital administration board, in an attempt to solve all the pending issues which were disallowing the progression of the office activities.

An important milestone was the first time the site was chosen to develop a clinical trial. I had to prepare the submission to competent authorities and to the hospital administration board. I contacted the PI and all involved services in order to complete the site facilities declaration. I needed information on characteristics and availability of the resources that would be used, and also information on the personnel that would constitute the trial staff.

At that time the close collaboration with other sites of the Blueclinical network was essential as I had never prepared a submission. All the documentation common to the all sites was only filled in once and then distributed between the Blueclinical offices. Due to this clinical trial, I was present at a two days Investigators' Meeting at Barcelona. During the meeting, the study was discussed in detail as well as the protocol procedures and safety issues. As this was an international meeting, it was possible to share experiences between study sites.

While at CHTV I started the distribution of the interest and capacities on clinical research questionnaire. It was a questionnaire developed by Blueclinical, with the intent of knowing which medical areas fitted the physicians' interests, and also the physicians that intended to work with the clinical research office. This task allowed me to know many physicians in a short period of time. The first questionnaires were sent by e-mail after a meeting with some physicians. Although they provided their answer in a short period of time, I realized that this was not a good strategy as there are many services and I had not the chance to schedule all the meetings in the time frame I had to have an answer from every physician. Afterwards, I talked personally with all service directors asking them to collect the contact of all physicians and whether they prefer to have the questionnaire in paper or online. This strategy had a positive outcome as I was able to have sixty answers in only two weeks.

One month after I started working at CHTV, as a consequence of a Blueclinical's strategic decision I began working homebased, going to the hospital when it was necessary. Meanwhile I also had to go to CHCB on clinical trials visits days to support the local CRC. At CHCB, usually three or four patients were scheduled for the same day. Unlikely at CHVNG/E, I had to process the blood samples. For this process, the time of clotting of each tube and the centrifugation velocity had to be considered. It is also necessary to make sure that samples of each patient are not mixed up or contaminated. At this site it was necessary go to the pharmacy with patients so that the drug compliance was calculated, and if there was missing or extra tablets the patient can explain what happened.

While I was home based I had a more theoretical job, as the tasks I did were translations, worksheets to clinical trials and review of standard operation procedures. All the projects I was involved at CHTV, like the submission procedure, and the interest and capacities on clinical research questionnaires were on hold.

After a month working home based, and as there was no prevision of when the hospital is going to make a decision about the collaboration with Blueclinical, it was decided that I was moving to the Blueclinical back office where I could be more useful. So the last month of my curricular training was spent at the back office.

Over there I did not have a project that was of my own responsibility. The tasks I performed belonged to someone else project. I helped my colleagues with the creation of a tool to control the sponsors' payments, the development of worksheets for different studies and the translation of some documents. The activity that differ the most of what I had previously done was the construction of a TMF. When I was at hospitals, the CRA delivers the TMF already completed during the initiation visit and I only had to keep it updated. To perform this tasks, first of all, and as for me it was a new task, I identified what are the documents necessary to each section. Then I requested them to my colleagues, and then archived them on the TMF.

3.3. TRAINING

Training is an essential part of the professional world. As a study coordinator training in protocols is mandatory, as well as in GCPs and in sample shipping. Training in protocols is provided by sponsors prior to the study initiation, or when the study is already ongoing, prior to the start of the collaboration, normally in person. At the end of each in person training session, I had signed a training log, where I confirmed I had been trained at the protocol. E-learning training usually regards the CRF and safety information and reports. At the end of the e-learning I habitually obtained a certificate that has to be sent to sponsor.

Blueclinical provides training curricula to all its staff, regarding, for example, legislation and team building activities. Even before I started my training program, I was present at a training day at Blueclinical phase I headquarters. The meeting purpose was "Because People Matter: Building a Team!", and it happed on the day of the first anniversary of Blueclinical. That was the first time I met with all Blueclinical staff, even though I already knew some people. During that day, we presented ourselves, learned about the Blueclinical History, Functional Areas, Values and Standards; Quality Management; Client Focus and Effective Communication.

At the beginning of September, Blueclinical team grown up, and four training days with all the Blueclinical business areas, were schedule. I missed the last day of training as I went to an investigators' meeting. The training focused the legislation applicable to clinical trials and to the development of medical devices, data management, the stages that a clinical trials goes through at a site and the R&D process.

In middle February there was another training meeting, this time only for the CRP staff. The objectives of the meeting were knowing the status of each office and identify strategies to solve troubles and improve the work being done.

On the 1st of October I was present at a workshop about GCPs organized by University of Aveiro. At the workshop, GCPs were focused on a practical perspective, as real examples were given.

4. DISCUSSION

In this chapter I am going to describe how the activities I developed during my internship contributed both for my personal and professional growth, what were the major difficulties I have faced, as well as what were the major achievements. I will review the activities I had performed, regarding what I had learned while doing them, and how my academic background contributed to their realization.

My internship was the first time ever I have contacted with the professional world. Although I theoretically knew that it is completely different from academia, the support of my colleagues and of the Blueclinical COD was essential to my adaptation. My academic background was a valuable tool during the internship even though it was always focused on a theoretical perspective of clinical trials. The knowledge on legislation, essential documents of a clinical trial, and product life cycle, allowed me to easily understand the reasons why some tasks are needed and to recognise the steps to perform next. In some situations the lack of a practical background was a disadvantage, making harder facing unexpected situations, for example. Other advantage of my academic background was the autonomy acquired with the problem based learning (PBL)[2], as it makes students look for answers instead of teachers provide all the information. This method provided me skills on search and data presentation that were useful during my training. When I was asked to perform a new task, firstly I tried to understand what was being asked, what the purpose of the task was, and then how I could accomplish it.

Time management was an important task, and maybe the one I have most improved during my internship. I learned that the first step is to calculate the time I expect to need to perform a task. Then, if I have more than one task to do at the same time, but I have no opportunity to do them all, I have to prioritize the tasks, doing first the one that is most important and most urgent. I did not feel that I needed a tool to help me prioritizing and estimating times, however I felt that a to-do list was essential. Now I have a calendar where I list every task I need to do and based on that, I, day by day, plan my activities.

[2] PBL is characterized by twice a week sessions, where during the first session a problem related with the course is presented and discussed, with participants having no or little knowledge on the subject. At the end of the session questions and learning objectives are defined. On the second session, after autonomous research work, the answers to the questions previously developed are presented.

Then, I learned that I had to have flexible timetables. On one hand, I have to adapt my timetables to the physicians' availability. My regular working timetable was between 9 am until 18 pm, with an hour to lunch. Although if physicians only have free time outside that schedule I went to the hospital earlier in the morning or stayed after hours, or had a smaller lunch break. On the other hand, patients' visits usually take longer than expected, so on visit mornings I did not plan to do any other tasks, even if there was only one patient. When visits had a duration minor than expected, I performed some of the pending tasks. Usually there were unexpected tasks, for instance physicians that needs help, the administration that asks for a new table, so, whenever it was possible, I tried to do every task not close to the deadline so I could managed unexpected situations.

Another thing I have learned was to be more organized. My job involves a lot of paper, so I needed to be as organized as possible to keep every document up-to-date and not to lose any document. At the office I have created my own dossier where I archived every documents that I use to prepare the patients' visits. All the important documents that were under my responsibility, were also archived on that dossier, until I had the chance to archive it on the right place or to give it to the intended person. All the documents I have created include the date of its creation in footnote, so it was possible to identify the versions of the document and assess if I was using the right version. When a new version of the study protocol was released I had to update my dossier, in order to be sure that I was using the most recent information available.

Organization is also critical since I was responsible for more than one protocol. Every protocol has its own specifications, and I could not mix up the specifications of each protocol. As it was impossible to know every specification I had pocket size protocols that I carried for every visit so that I could clarify every doubt I or the physician had. Worksheets also had to have the study identified so I easily recognized them, and only use the right worksheet with the right patient. It was also essential to know which physician is assigned to each patient, so that issues related with subjects were only discussed with his/her physician.

Also regarding organization, I created a secured document to store access information regarding the online pages of the studies. Each study has at least two websites that I need

to access frequently, and each website had different access credentials so I created that document to warrantee that I knew how to access all the websites.

Developing templates made me think out of the box to achieve useful and easy-to-use documents. Some templates, such as the concomitant medication worksheet, were the result of difficulties I felt. In the case of concomitant medication, I had patients that have more than 10 different drugs every day, and the physician usually forget to write down some of those drugs, so I need a tool that allows having medication under control and knowing exact information about it, such as the onset and offset date.´

At the beginning of my internship, reading and understanding study protocols was sometimes difficult, due to the language used. Also, the protocol organization depends on the sponsor. With training, it was possible to easily recognise which is the section where the information I was looking for is.

As a CRC, I had to contact with several people – study teams, sponsor's representatives, patients, patient's relatives. Due to this I had to overcome the lack of self-confidence and the stress I felt when I had to talk with other people. At CHTV I had a few stressful situations, as I had to face negative opinions about the clinical research office (at CHVNG/E it was the clinical research manager that faced those opinions, so I never had to directly deal with them). Those were challenging situations, that made me realized that I had a lot to improve regarding the opinions of other people. Since then, in similar situations, I try to better evaluate what is being said and use better arguments to support my point of view.

Talking to patients was also challenging. On one hand medical issues had to be discussed with physicians and it was not my job to talk about them with patients or their relatives. Although patients frequently asked me questions that lead to medical issues so I had to tell them to talk directly with the physicians. Patients could misunderstand anything I said so I had to be really careful while choosing the words I was going to use.

Patients participating in clinical trials have to go frequently to the hospital, sometimes more than once a month. I accompanied them at every visit, trying to make their experience at the hospital easier. Following patients, made me aware of their health status,

and sometimes I knew before them that they were relapsing, or that the tumour was getting smaller, for instance. During my internship, the health status of the patient, to whom I first prepared the screening and randomization visits all by myself, quickly deteriorated, and the patient died only a few months after randomization. This had affected me as I was not prepared to face death. I understood that I needed to improve the way I interacted with patients, keeping a distant relationship with them, so that, in future I would not be so affected by their health or death. I do not exactly know how to improve this aspect, as I think that gaining more experience is the best way to progress. Even though, taking part of workshops regarding how to behave with patients is an option that I will take in consideration in short term.

As far as GCP's compliance is concerned, I felt some difficulties. Physicians knew what GCP's are and knew that they have to conduct clinical trials in compliance with GCP's and protocols, nevertheless it was hard to make them perform tasks according with GCP's. For example, GCP's stated that when a mistake is done in a handwritten paper it could be solved by crossing the wrong information out, write the right one, sign and date. Physicians never remember to sign and date and usually scratch the wrong information, not allowing it to be read. Another problem was the AEs. Some physicians do not understand that every AE is important, even if it is not related with the experimental product. I could only overcome these problems with persistence, and patience. It was interesting to observe how some physicians, as the time went by, became more aware of what they needed to do, to follow the protocol and GCP's. Understanding physicians' hand-write was challenging. Only practice, and reading the patient files every week allowed me to be more expedite understanding the abbreviations used and the calligraphy.

Regarding my training objectives, I have not achieved all of them. The objectives that are not related with the company were, in my opinion, achieved. Now I have a more fluent speech, both in English and in Portuguese, and I am able to organize my ideas before starting to speak. My written skills improved, as now I am more precise and brief. As described above, I used the knowledge acquired in my degrees in various situations.

Through my training I realized I was becoming more autonomous, and organized. My self-confidence has increased, although I did not always felt confident. My team group working

skills have improved, and being part of Blueclinical was a great influence in this aspect, as the company boost team work.

Contacting with different CRA's allowed me to develop my professional network and also know some information about other pharmaceutical companies.

During my training I have understood what the steps to implement a clinical research office were, and how difficult this task could be, as it depends on many people, that not always agree with the project or that simply do not care about it. It is necessary to be persistent and not let that issues are forgotten.

I was also able to know how to plan, conduct and coordinate a clinical trial and an observational study, excluding the close-out visits. I participated in every step since the submission preparation until the patients' visits. The submission tasks were the tasks I contacted less with, although I think I will be comfortable performing a submission whenever necessary. Patients' visits were, without doubt, the task where I gained more experience. During my training I worked mainly with protocols on cancer, and I believe that was an advantage, as these protocols usually are the more complex ones.

I think I have acquired basic knowledge in monitoring tasks, as I was present in various monitoring visits, and some of the CRA's have shared their experience. I do not feel I have the necessary knowledge to perform a monitoring visit, although now I know that a monitoring visit could regard for example source documents verification and medication reconciliation. At the end of the visit a monitoring report has to be developed and the protocol deviations, corrective actions and pending issues communicated to the site.

I developed a good relationship with the physicians and other clinical trial personnel I worked with, although I do not know if I increased their motivation to perform clinical trials. There were moments where I felt that they were motivated and liked to do research, when for example they not only signed a document but also asked information regarding the study. Nonetheless, there were other moments when it seemed as they prefer not to participate in clinical trials. This happened when they, for instance, transformed a small problem into a big one. On the other hand, I felt that I positively influenced some elements

of the staff to be GCP compliant. I believe that both the motivation and the GCP compliance are factors that have to be worked every day, and changes happen slowly.

As far as the relationship with the Blueclinical staff is concerned, I believe I fully achieved the proposed objective as I have a positive relation with all of my colleagues. I established closer contact with the CRP staff, even though each of us is based at a different hospital. Digital tools, such as e-mail and instant messaging services are frequently used to keep in contact and to ask for clarifications or help.

I failed to achieve the objective about inspections and audits and the one about financial agreements. As none of the clinical trials I coordinated was submitted to an inspection or audit I had not prepared the site to these activities. However I have realized that preparing a site for an audit/inspection is an ongoing job, as it is necessary to do our best, minimize mistakes and protocol deviations and implement corrective and preventive actions, every day. Studying protocols and creating worksheets were tools I used as an attempt to reduce mistakes.

During my internship I was not focused on the submission process, so I did not had the opportunity to review and improve the financial agreements between sponsors and hospitals. Although I learned that the financial agreement must include information about the payment of patients' expenses and of unscheduled visits. Regarding the patients' expenses, the value defined must be in accordance with the influence area of the hospital, as a patient could not be penalized for living far away from the hospital.

5. CONCLUSION

Overall, thinking about what I have done, learned and experienced during my internship I have to assume that it was more than I have ever imagined. I am sure I had developed several skills, both hard and soft skills, which will be very valuable during my career.

Almost every day I had to interact with someone I had never met before, or to perform a new task, or to solve an unexpected issue. Not knowing exactly how the following day would be, what challenges I would have to face next, was a positive aspect of my training.

The pharmaceutical industry has been affected by the present economic crisis, and is facing changes in the R&D paradigms. Being able to adapt to different work environments will be a key characteristic for everyone working in this area. I think that during my training I started developing these characteristics as in a short period of time I was present at different institutions, each one with its own peculiarities.

During these ten months I had the opportunity to contact with the professional world, know the realities of different hospitals, and also the reality of working at an office. All the difficulties I faced were overcome with hard working and with the support of my colleagues. I still do not feel ready to survive in the professional world, but the experience acquired during this period has an incalculable value to my future, and used in the right way will allow me to have a successful career.

My internship was a remarkable period and overall the majority of my objectives were accomplished, however not always fully accomplished. I still have a long learning journey, and both my hard and soft skills have much to improve.

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