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ANA CLÁUDIA MARQUES SALGUEIRO

Estágio em Coordenação de Ensaios Clínicos numa Unidade de Investigação Clínica

Training in Coordination of Clinical Trials in a Clinical Research Unit

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Estágio Curricular em Coordenação de Ensaios Clínicos num Centro de Investigação Clínica

Curricular Training in Coordination of Clinical Trials in a Clinical Research Unit

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Medicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Auxiliar da Faculdade de Medicina da Universidade de Lisboa e da Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este trabalho às pessoas que sempre estiveram presentes na minha vida e que me ajudaram a alcançar os meus sonhos.
Que sempre me ensinaram, sempre me apoiaram e sempre acreditaram em mim.

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Sem o vosso apoio esta etapa seria bastante mais difícil.

“O essencial é invisível aos olhos!” by Antoine de Saint-Exupéry

o júri

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palavras-chave

Mestrado de Medicina Farmacêutica; Ensaios Clínicos; Estudos Obervacionais; Investigação Clínica; Centro de Investigação Clínica; Coordenação de Ensaios Clínicos; Farmacovigilância; Monitorização

resumo

Este relatório descreve as actividades e projectos desenvolvidos no âmbito de estágio curricular numa unidade de investigação clínica, o Centro de Investigação Clínica (CIC), liderada pelo Professor Doutor Joaquim Ferreira. O CIC faz parte dos grupos de investigação do Instituto de Medicina Molecular (IMM) inserindo-se na iniciativa do consórcio Centro Académico de Medicina de Lisboa (CAML).

A principal área de estágio foi a coordenação de ensaios clínicos e estudos observacionais. Adicionalmente foram abordadas outras actividades durante o estágio, tais como farmacovigilância, monitorização, preenchimento de bases de dados, escrita científica e algumas actividades de coordenação a nível nacional de estudo observacional europeu sobre a doença de Huntington financiado por European Huntington's Disease Network (EHDN).

Refere-se no estado da arte o Processo de Investigação e Desenvolvimento de novos medicamentos e caracteriza-se alguns aspectos da investigação clínica em Portugal incluindo vantagens na organização de redes clínicas de investigação.

Ao longo do estágio, com 10 meses de duração (início a 1 Setembro de 2013 e fim a 1 de Julho de 2014) aprofundei o conhecimento na área de investigação clínica, percebi a importância de unidades de investigação clínica, a importância e papel de coordenadores clínicos e expandi as minhas áreas de interesse. O treino específico centrou-se em estudos clínicos na área da neurologia, nomeadamente ensaios de clínicos de fase II e III, e estudos observacionais.
Tive ainda oportunidade de compreender a realidade prática e logística da condução de estudos clínicos num centro de investigação.

Considero que este estágio foi uma experiência valiosa de introdução á prática de investigação clínica. Desta forma, termino o estágio com motivação e interesse em trabalhar na área de coordenação ou monitorização de estudos.

keywords

Master's Degree in Pharmaceutical Medicine ; Clinical Trials; Observational Studies; Clinical Research; Clinical Research Unit; Coordination of Clinical Trials; Pharmacovigilance; Monitoring

abstract

This report describes several activities and projects developed in the context of a curricular training in a clinical research unit, Centro de Investigação Clínica (CIC), led by Professor Joaquim Ferreira. The CIC is one of the research groups of Instituto de Medicina Molecular (IMM) and it is also a group of the Centro Académico de Medicina de Lisboa (CAML) consortium.

The principal area of training was the coordination of clinical trials and observational studies. Additionally, other research activities were conducted during the training such as, pharmacovigilance, monitoring, data entry, medical writing and some language coordination activities in a European observational study about Huntington's Disease founded by European Huntington's Disease Network (EHDN).

It is mention on the State of the Art the Research & Development Process of a new drug and it is characterised some issues about clinical research in Portugal, including advantages in the establishment and organisation of clinical networks.

During the training, with the duration of 10 months (that started on 1st September 2013 and finished on 1st July 2014) I deepened my knowledge in clinical research area, understand the importance of the clinical research units, the importance and the role of the study coordinators and expand my areas of interest. The specific training focused in neurological clinical.
I had opportunity to understand the practical and logistical difficulties that a research unit faces during the conduction of clinical studies

I consider that this training was a valuable experience of introduction of the practice of clinical research. I finished this training with the motivation and interest in working in the area of coordination and monitoring of studies.

"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skilful execution; it represents the wise choice of many alternatives!" *William A. Foster*

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
CAML	Centro Académico de Medicina de Lisboa
CHLN, E.P.E. - HSM	Centro Hospitalar de Lisboa Norte, E.P.E. – Hospital Santa Maria
CRF	Case Report Form
CRU	Clinical Research Unit
CT	Clinical Trial
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EHDN	European Huntington's Disease Network
FAP	Familial Amyloid Polyneuropathy
FCT	Fundação para a Ciência e a Tecnologia
FMUL	Faculdade de Medicina da Universidade de Lisboa
GCP's	Good Clinical Practices
ICF	Inform Consent Form
ICH	International Conference of Harmonisation
IMI	Innovative Medicines Initiative
IMM	Instituto de Medicina Molecular
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde I.P.
ISF	Investigator Site File
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFCT-FMUL	Laboratório de Farmacologia Clínica e Terapêutica da Faculdade de Medicina de Lisboa
OS	Observational Study
PI	Principal Investigator
R&D	Research and Development Process
SC	Study Coordinator
SIAHS	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SIV	Site Initiation Visit

SNF	Sistema Nacional de Farmacovigilância
URF	Unidades Regionais de Farmacovigilância
URFLVT	Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo

1. Introduction

This report describes my curricular training carried out during the second year of my Master's degree in Pharmaceutical Medicine at the University of Aveiro, which is affiliated to the PharmaTrain programme (1). This training was developed in the clinical research area and lasted for about 10 months.

I initiated the training on 1st September 2013 in Unidade de Farmacologia Clínica, a group of Instituto de Medicina Molecular (IMM), that is a part of the CAML – Centro Académico de Medicina de Lisboa. The CAML is a consortium made up of three entities: Centro Hospitalar de Lisboa Norte, E.P.E. – Hospital Santa Maria (CHLN, E.P.E. – HSM), the FMUL (Faculdade de Medicina da Universidade de Lisboa) and the IMM (2). Due to the characteristics of the host institution, during the training I had the opportunity to work in several departments.

Throughout the training I had the opportunity to be brought into contact with many areas related to research and development of new drugs. Initially I developed activities, such as coordinating studies, co-monitoring an observational study (OS), managing and processing data of an OS and later I participated in pharmacovigilance activities in Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo (URFLVT) and in medical writing activities. All the activities performed during the 10 months of training were supervised by Professor Joaquim Ferreira, Group Leader of the Unidade de Farmacologia Clinica; Director of Laboratório de Farmacologia Clínica e Terapêutica da Faculdade de Medicina de Lisboa (LFCT-FMUL) and Director of Centro de Investigação Clínica (CIC).

Initially I defined some primary objectives and when I was introduced specifically to Unidade de Farmacologia Clínica I realised the possibility of complementing my training and I defined others objectives - the secondary objectives. At the end of training I verified if my personal and professional goals were achieved.

The primary objectives defined for my training were:

- To acquire skills in clinical research coordination;
- Perform daily activities as a Study Coordinator (SC);
- To apply and complement the previously acquired academic knowledge in a clinical research context;
- To gain knowledge with the extensive experience and skills of senior professionals;

- To understand the functioning of a clinical research unit (CRU);
- To know and better understand the CRU daily problems during the CTs (Clinical Trials);

As it was mentioned above, a set of secondary objectives were also established:

- To know the principal daily activities of a regional pharmacovigilance unit;
- To contact and learn about the monitoring world in the context of clinical research;
- To establish a working contact network;
- To identify potential areas of professional interest within the pharmaceutical industry;
- To develop and improve personal and soft skills, such as communication, self-confidence, critical thinking, problem solving, organisation, autonomy and responsibility;
- To write a paper related to the area of CTs and practice medical writing skills;

This report is organised in 7 main sections: 1. Introduction; 2. Host Institution Overview; 3. State of the Art of Clinical Research; 4. On the job training; 5. Discussion; 6. Conclusion and 7. References.

The first section, Introduction, explains the context, characteristics and objectives of this report.

The second section, Host Institution Overview, describes the host institution, the history, characteristics, organisation, its vision and relation with other organisations.

The State of the Art of Clinical Research, the third section, presents some information about Research and Development (R&D) process of new drugs, clinical research in Portugal, CTs, the regulatory environment, the importance of CRUs and clinical research networks.

The fourth one, On the job training, is made up of a generic and specific training. This section describes the education received at the beginning of this training and the activities I performed in CIC as a SC and a monitor. Additionally, it presents data management, pharmacovigilance and medical writing experience and activities.

The fifth, Discussion, presents the knowledge and lessons learnt during the training and the next section, sixth section, Conclusion, is characterised by a conclusion of the activities performed during the ten months of training and my performance.

The final section, the seventh, denominated References, is constituted by a list of bibliography used as support.

2. Host Institution Overview

This section describes the activities performed by the host institution, its goals, structure and relation with other institutions. The host institution is included in a consortium that integrates several institutions (2). The main goals of this consortium are to promote and encourage the research. The IMM is considered one of the principal Portuguese biomedical institution with a wide range of international recognition (3, 4). Throughout the years, the institution has been constructing several relationships with national and international entities (3), and some of them are described below.

2.1 Instituto de Medicina Molecular

Instituto de Medicina Molecular (IMM) is a private and non-profit association dedicated to research (5). It is an institution of Universidade de Lisboa located in the campus of Faculdade de Medicina de Lisboa, Portugal. It was founded in December 2001 as a result of the association of research units from the FMUL and CHLN, E.P.E. – HSM, such as "Centro de Biologia e Patologia Molecular", "Centro de Neurociências de Lisboa", "Centro de Microcirculação e Vascular Patobiológica", "Centro de Gastroenterologia", and the "Centro de Nutrição e Metabolismo" (5). Later, in 2003, the "Centro de Investigação Molecular Patobiológico from Instituto Português de Oncologia Francisco Gentil" joined IMM, although only in 2004 they initiated the research activity together.

Currently, the IMM is one of the main research institutions of science in Portugal with highly international recognition (3). This success is mostly due to efforts between some institutions, such as Faculdade de Medicina, Centro Hospitalar Lisboa Norte, collaboration of

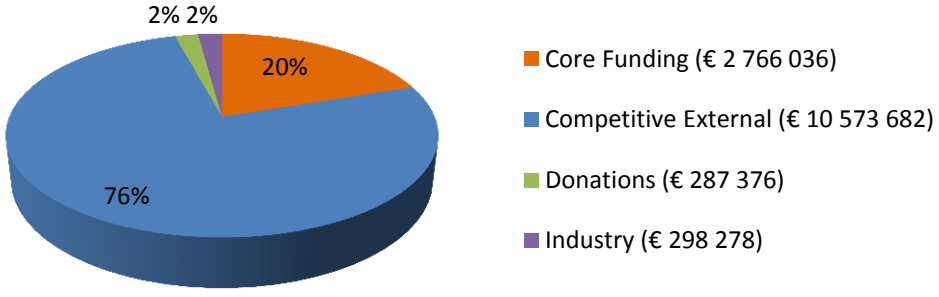

Figure 1 Expenditure in 2013 by Funding Source (2013) (3, 4)

many networks and international funding (5, 6).

The IMM is an institution supported by funds obtained from peer reviewed competitive grants, private donations and industrial partnerships (national and international) (3). In 2013, IMM spent a total of € 13,925,388 in research (3). According to Activity Report 2013 and IMM Report 2013 most of the expenditures, specifically € 10,573,698 (76% of the total expenditures) were supported through competitive external (3). (Figure 1)

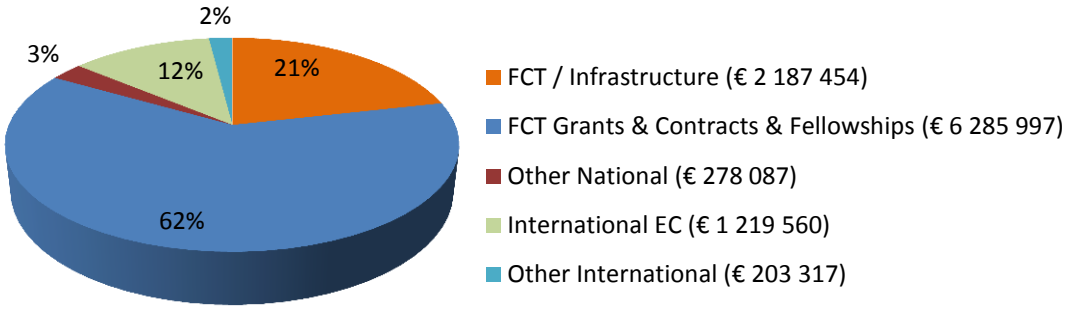

Figure 2 Competitive external funding of IMM (2013) (3, 4)

The competitive external research funding is ensured though several entities. The principal contribution was by Fundação para a Ciência e a Tecnologia (FCT)-Grants, contracts and fellowship followed by FCT-Infrastructure, International EC, and other national and international institutions (3). (Figure 2)

The IMM mission is to promote to the biomedical population the basic, clinical and translation research according to an innovative pattern. As a result of this, the main goals are to better understand the diseases, contribute to the development of diagnostic or prevention tools and develop efficient therapeutics (5). Furthermore, this institution also "supports the scientific

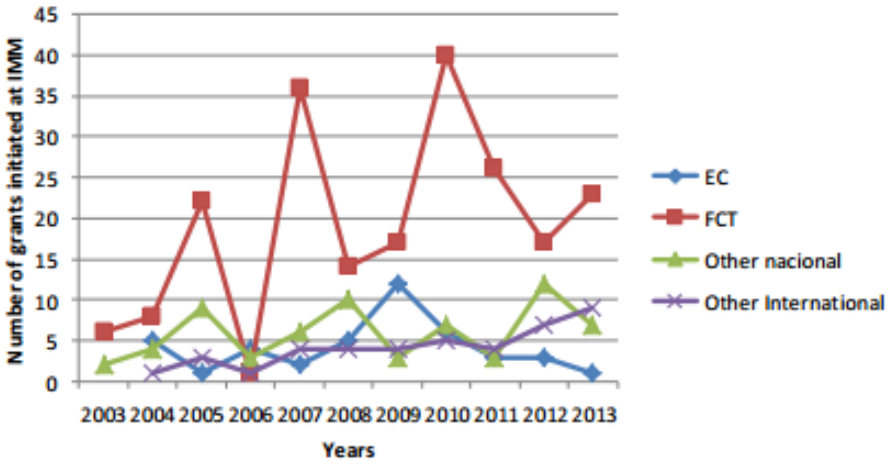

Figure 3 Number of Research Grants Initiated at IMM (2003-2013) (3, 4)

education, scientific diffusion and provision of services in specialised diagnostic areas, and quality control and it collaborates with national and international health commissions" (7).

Due to the fact that the IMM has the objective of promoting scientific advancement, over the years IMM, with the help of some international and national entities has conducted many research grants (3). Specifically in the last year, IMM had 285 research grants on-going. Despite the decrease in the number of research grants initiated by year, since 2012 it has been verified a mild recovery. Public National FCT and some others international institutions could increase its investment a little, but unfortunately the Public European Commission and national institution has not recovered yet (3). (Figure 3)

As a result of hard working in 2013 the IMM papers were cited 4482 times, IMM researchers published about 300 papers in international journals (Figure 4), developed some international book chapters (about 20), did communications in international (about 352) and national conferences (about 231), organised seminars and conferences (about 380), organised conferences (about 64), won several international awards and registered some patents (about 5) (3, 7). According to 2013 IMM Activity, during the last year there was an increase of IMM papers cited in Journals and a decrease of papers published. Between 2012 to 2013 publications in international journals with an impact factor between 5-10 decreased whereas publications in international journals with an impact factor higher than 10 increase (3). (Figure 4 e 5)

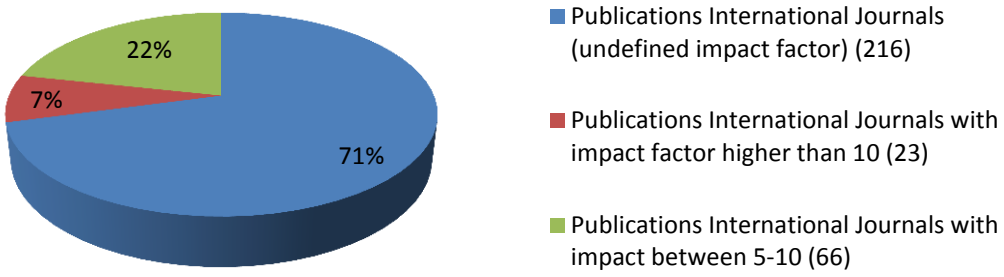

Figure 4 Number of Published Papers in 2013 according to impact factor (3)

In 2013, 36 research labs, 4 start-ups and about 457 researchers (217 with PhD, 83 PhD students, 43 MSc students, 114 Bachelor students) and 37 international research fellows were distributed among three research programs: Cell and Development Biology, Immunology and Infection, and Neurosciences. In order to help its researchers, IMM also provides a series of services that includes training, support and research (3). IMM offers equipped state-of-art flow

cytometry, bio-imaging, animal facilities (fish and rodents) and bio-bank facilities. In addition, IMM also offers scientific seminars and international PhD and MD/PhD programmes (7).

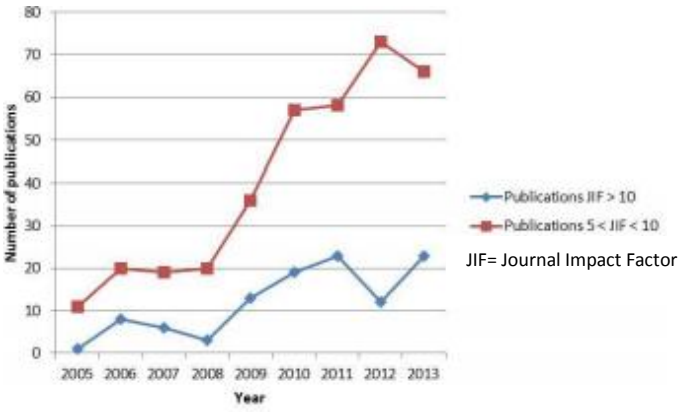

Figure 5 IMM Publications in international journals (JIF>10 and 5<JIF<10) (3)

2.2 Unidade de Farmacologia Clínica

The LFCT-FMUL is a physical space which belongs to FMUL where the Unidade de Farmacologia Clínica (which is a subgroup of IMM) operates.

The Unidade de Farmacologia Clínica was officially created on 1st July 2013 and it is made up of URFLVT, CIC and the Cochrane Review Group.

The principal mission of the unit is to contribute to the development of effective and safe therapeutic interventions through optimised methodologies for design, conduction, analysis and report of CTs (3). The main research areas are Parkinson's Disease, Huntington's Disease, Movement Disorders, Neuropharmacology, CTs and Systematic reviews. And the principal pharmacology domains of interest are CTs methodology, outcomes, systematic, reviews, safety and drug use (3). (Figure 6 represents the organization of IMM, with special highlight to the unit where I did my training - Unidade de Farmacologia Clínica).

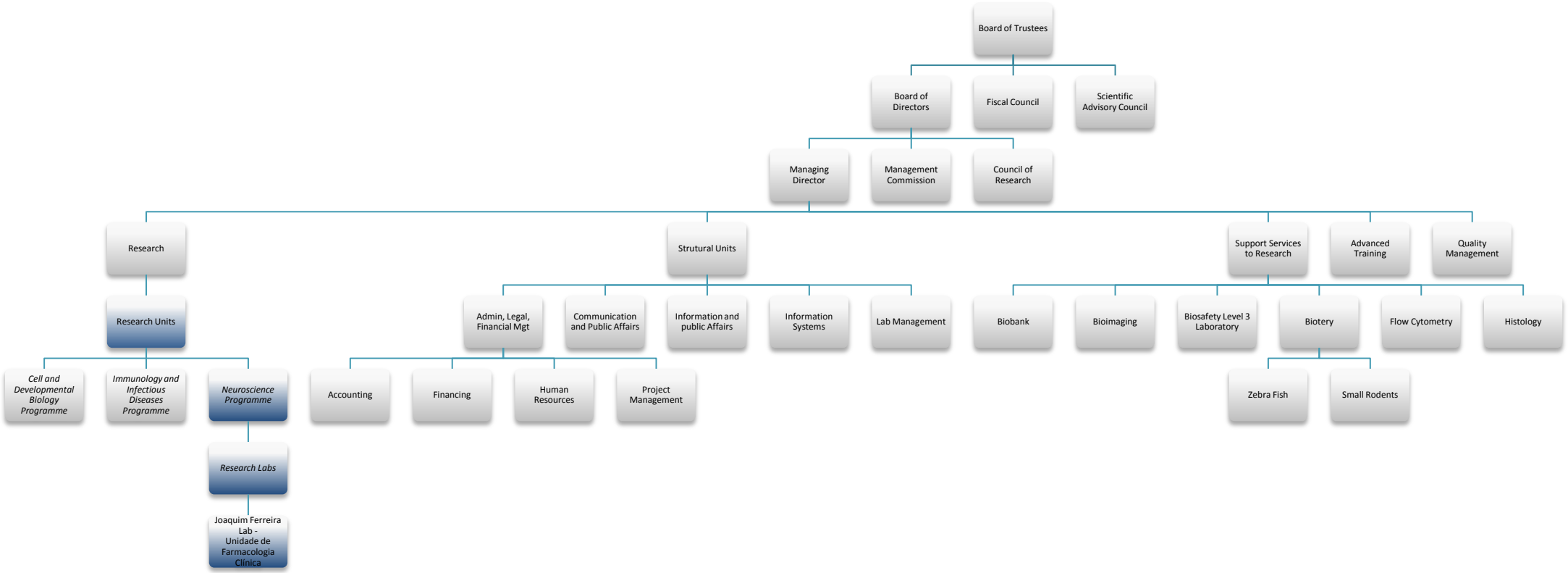

Figure 6 Structure and Organisation of IMM (3)

2.2.1 Sistema Nacional de Farmacovigilância

In order to ensure the proper functioning of the national health system the Autoridade Nacional do Medicamento e Produtos de Saúde I.P. (INFARMED) created subsystems with different activities and missions. Thus, in the context of pharmacovigilance the Sistema Nacional de Farmacovigilância (SNF) was created (8).

Later (in 2000) the system decentralisation occurred with the objective of approaching the SNF to the health professionals in order to improve the technical and scientific capacity in pharmacovigilance, to disseminate the system and encourage the notification of Adverse Drug Reactions (ADRs). Throughout the decentralisation process for regional units emerged - Unidades Regionais de Farmacovigilância (URF) (8).

At the moment there are 4 regional units: Unidade Regional de Farmacovigilância do Norte, Unidade Regional de Farmacovigilância do Centro, Unidade Regional de Farmacovigilância do Sul and Unidade Regional de Lisboa e Vale do Tejo (URFLVT).

I only had the opportunity to be in contact with URFLVT, located at LFCT-FMUL that covers the corresponding population to health regional administration of Lisboa and Vale do Tejo region, about 3,659,868 inhabitants (public survey according) (9). I was working in this unit only for one month but it was enough to realise the great responsibility and importance of its existence and activities.

The goal of the unit is to monitor the safety of commercialised medicines through the promotion and dissemination of safety control methods, especially in relation to spontaneous reports of ADRs (10). Hence, the unit detects, collects, registers, processes and evaluates the data of post-commercialised medicines which later allows a timely intervention of competent authorities to ensure the quality and safety of medicines (11).

In addition to the aforementioned this unit still writes periodic reports about new ADRs; makes proposals for epidemiological studies; prepares important data to other regional units or national and international authorities; plans and executes actions on pharmacovigilance training; and performs additional activities asked by SNF (10). All these activities have the mission to alert the community about the importance of reporting, to alert the possibility of the occurrence of ADRs and to explain the process of ADR assessment (11).

The figure below shows the ADRs processed from 1992 to 2013 (Figure 7) (12).

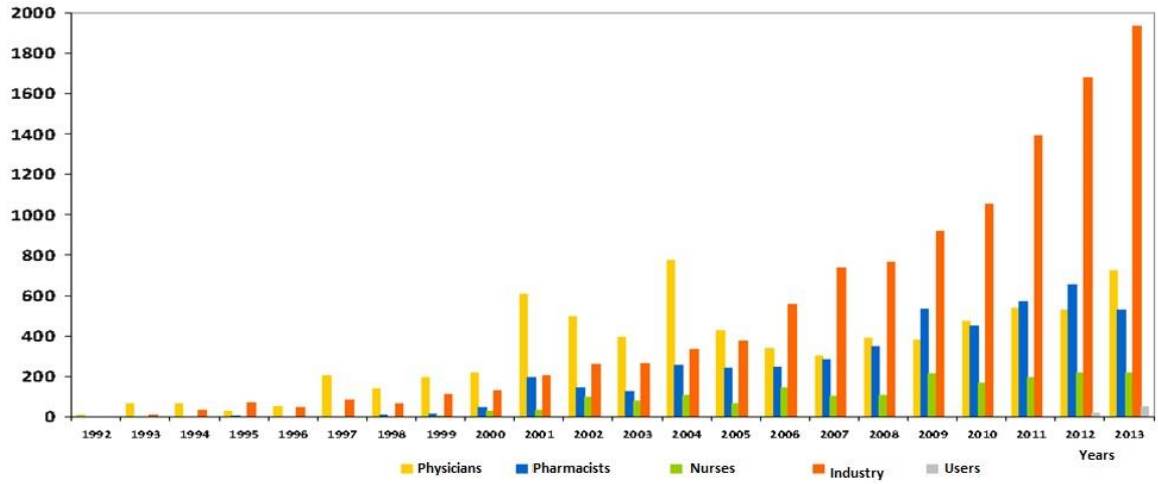

Figure 7 Number of ADR's received in SNF (1992-2013) (12)

2.2.2 Cochrane Review Group

Cochrane is an independent and international working group made up of institutions or individuals such as health professionals, researchers and patients. This collaboration is non-profit and operates in over 120 countries with the objective of producing accessible, credible and high quality health data (13).

The Cochrane Group is organised in several groups with people with interests to carry out systematic reviews. All these groups are managed by an edition team who reviews the work and that includes it in Cochrane Library. The task of this unit allows the development of data bases with reliable, updated, summarised and accessible scientific information (13).

The Unidade de Farmacologia Clínica has a group of people that work to Cochrane review group.

2.2.3 Centro de Investigação Clínica

The Unidade de Farmacologia Clínica is responsible for conducting research and doctoral programs. This unit creates knowledge, provides training to people in essential areas for the implementation and development of CTs, and encourages them to participate in clinical research.

When my training started, the structure of the unit had suffered some changes in a recent past, and because of that the new organisation is not official in the IMM webpage. My training was performed in a subgroup of Unidade de Farmacologia Clínica dedicated to clinical research,

called Centro de Investigação Clínica - CIC. The CIC was founded by Professor António Damásio and Professor Castro Caldas in 1969. Now the head of CIC is Professor Joaquim Ferreira.

The CIC is located on the 6th floor of CHLN, E.P.E. - HSM but it is a part of the Unidade de Farmacologia Clínica of IMM. Throughout the time the group had several structures and names. According to my search, in July 2012, the research group was called Clinical Neuropharmacology Group of Neurological Clinical Research Unit and only in 2013 was it called Centro de Investigação Clínica (CIC)(4).

In the beginning the main research area was "movement disorders" and due to that the group gained the sub-name of Movement Disorders. When the Movement Disorders Group was set up, the objective was only to conduct CTs in movement disorders. However, throughout the years the group expanded its capacities and became able and qualified to conduct CTs in other neurological disorders.

Throughout the time the main advantage of CIC was the strong collaboration among the experienced and qualified Principal Investigators (PI's), based on common clinical investigation methodologies and particular features of research expertise (14). The success and competence of CIC is essentially a result of multiple collaborations developed by the PI's with IMM, national and international major research centres and clinical networks specialised in areas of basic neurosciences, clinical genetics, advanced statistical methods, biological engineering, and neuroimaging (14).

The reason of success of the group is due to the multidisciplinary characteristics of the staff (15). The conduction of CTs implies a participation of participants (healthy or unhealthy) and diversified, competent and qualified health professionals. As a requirement there must be PI's among the health professionals (who are responsible for all the conduction of the research at site) (16).

Obviously, the patients have the central role of clinical research, and without them the research studies cannot be possible (17, 18). Regarding this aspect CIC is also fortunate; the CIC has a well-established recruitment, since the potential candidates are from CHLN, E.P.E. – HSM.

Clinical research is a very exigent and complex practice that is made up of many steps and activities (19). Doing clinical research is only possible due the strong working team and diversity of background by the members (15). Due to this nature many professionals and departments must be involved. In CIC I verified a very well established and defined working team. The research team

at CIC made up of elements with different background and expertise that complement each other.

The duties of each member were clear to everyone and because of that the activities were done according previously required and without errors. Thus, in addition to PI's, the unit also has other essential and qualified health professionals for CTs practice, such as co-investigators, SCs, pharmacists, study nurses, laboratory technicians and statistics technicians (Figure 8).

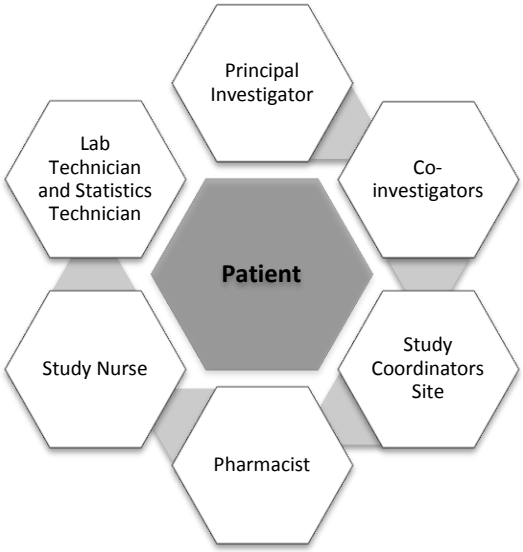

Figure 8 Staff in CIC

CIC it is a clinical research site which contains all the features for performing CTs according to the International Conference of Harmonisation (ICH) - Good Clinical Practice (GCP), only requiring an external intervention for some complementary exams required by sponsor. GCP is an "international ethical and scientific quality standard for designing, conducting and reporting of trials that involves the participation of human subjects" (16). This guideline ensures the rights, safety and well-being of trial subjects and the credibility of CT data (16). It is also the guideline which defines standards that the governments can transpose into regulations for CTs involving human subjects.

The unit has a monitoring room/meeting room where CRA could monitor data and we could have some meetings; a consultation room to evaluate the patients; an office where the SCs worked; and a sitting room where SCs and investigators could take a break; a room to collect samples of patients; an archive room; and a specific area in the hospital pharmacy for CTs (Figure 9) (20). There are also specific materials, such as computers with internet with restrict access,

medical calibrated material (for example tympanic thermometer, scales, blood pressure and electrocardiograph machines), material to collect biologic samples, processed and stored at ambient temperature or frozen, and calibrated centrifuge with temperature control.

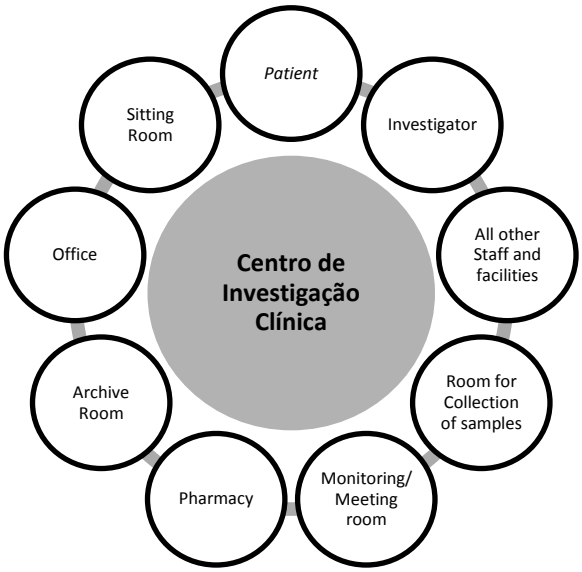

Figure 9 Operational Structure of CIC
(relation between physical spaces and clinical research staff) (3, 20)

The main mission of CIC is to conduct clinical research ensuring the rights and well-being of its participants to later improve patient's quality of life and offer the best treatment (16). The rigour and precision are the group's rules to produce quality data.

In order to characterise the activity and experience of CIC I searched in the hospital database and records of CIC.

According to my search the group started the activity in 1999 and it has been dedicating essentially to CTs. Throughout the time the unit has participated in a total of 139 studies (106 CTs and 33 OSs) (21). Parkinson's Disease is the principal therapeutic area of research with a total of 42 studies followed by Multiple Sclerosis with 37 studies conducted (21).

The CTs have been essentially conducted in Parkinson's Disease (38 CTs), Multiple Sclerosis (14 CTs), Alzheimer's disease (15 CTs), Epilepsy (13 CTs) and Familial Amyloid Polyneuropathy (FAP) (8 CTs). Since the beginning of its activities as a CRU until now Parkinson's Disease is no doubt the therapeutic area with the most CTs conducted, followed by Multiple Sclerosis (21). CIC conducted many CTs divided into 15 neurological disorders. As we can see in Figure 10, there is a significant number of CTs in neurological diseases.

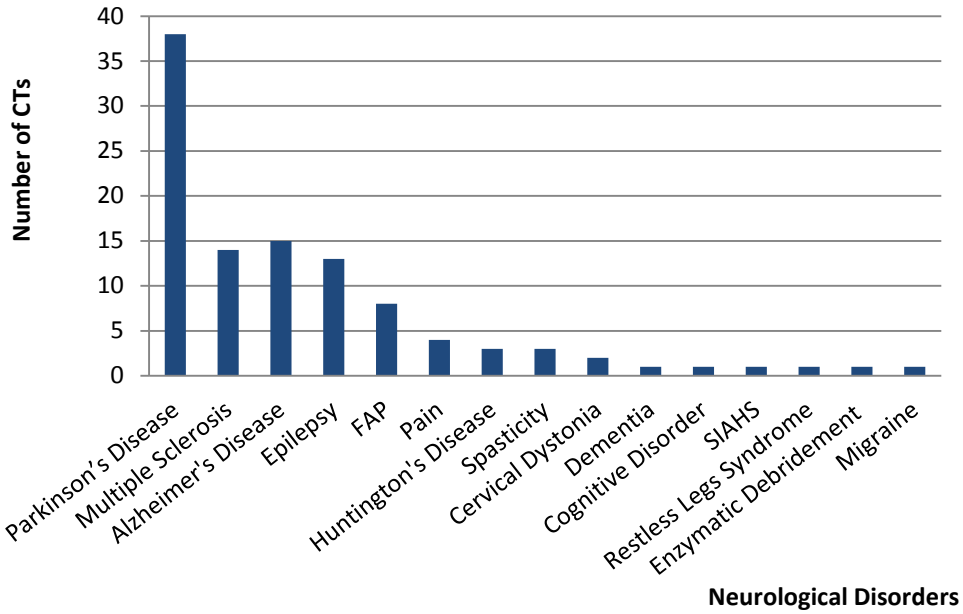

Figure 10 Number of Clinical Trials according to clinical area (1999-2014)
(FAP: Familial Amyloid Polyneuropathy; SIAHS: Syndrome of Inappropriate Antidiuretic Hormone Secretion)

According to data compiled CIC had experience in all CT phases but phase III is clearly the main phase of CTs conducted by CIC with a total of 69 CTs followed by phase II with 16 CTs (21). In phase II/III 7 CTs were conducted, phase IIB presents 6 CTs, followed by phase IIIB with 5 CTs and phase IV with 2 CTs and only 1 CT in phase I.

Regarding the number of OSs, the principal neurological disorder is Multiple Sclerosis and the second is Parkinson's Disease (21). In Multiple Sclerosis 23 CTs were conducted and in Parkinson's Disease 4 CTs were presented (Figure 11).

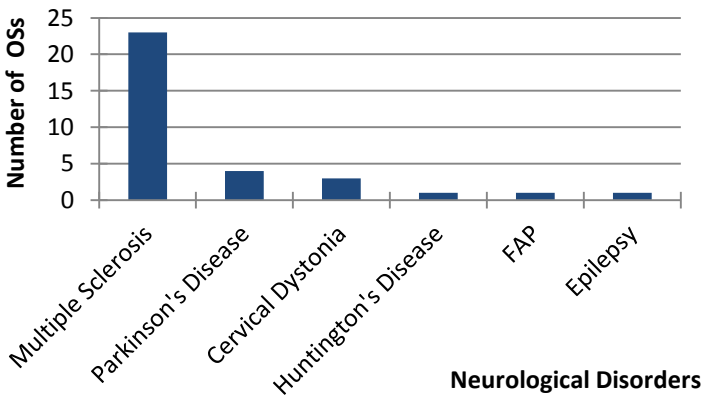

Figure 11 Number of OSs conducted at CIC (1999-2014)
(FAP: Familial Amyloid Polyneuropathy)

At the end of this training there were 20 CTs and 11 OSs on-going (Figure 12). The principal area was clearly the Multiple Sclerosis, followed by Parkinson's Disease and Epilepsy.

As I mention previously, to better understand the activity of CIC I did a small search. Initially I consulted some reports of CIC trainees and then I complemented the information with new data. Figure 10 is a result of the gathering of data from Training in Clinical Studies Coordination in a Research Centre, Rita Carreira (22) (since 1999-2011) and data from CIC database (since 2011 to 2014).

These data follow the previously reported trends, Training in Clinical Studies Coordination in a Research Centre regarding the numeric representation of principal pathologies areas and study phases. We have similar information about the target of disease and the main phase of CTs. Until 2011, CIC had a cumulative experience of 84 CTs. Presently this number has increased to a total of 139 studies (106 CTs and 33 OSs).

In the last years the unit has received more CTs than OSs. After discussing these numbers with the clinical research group, they indicated that this fact was an option of the investigators. They gave priority to CTs rather than observational studies.

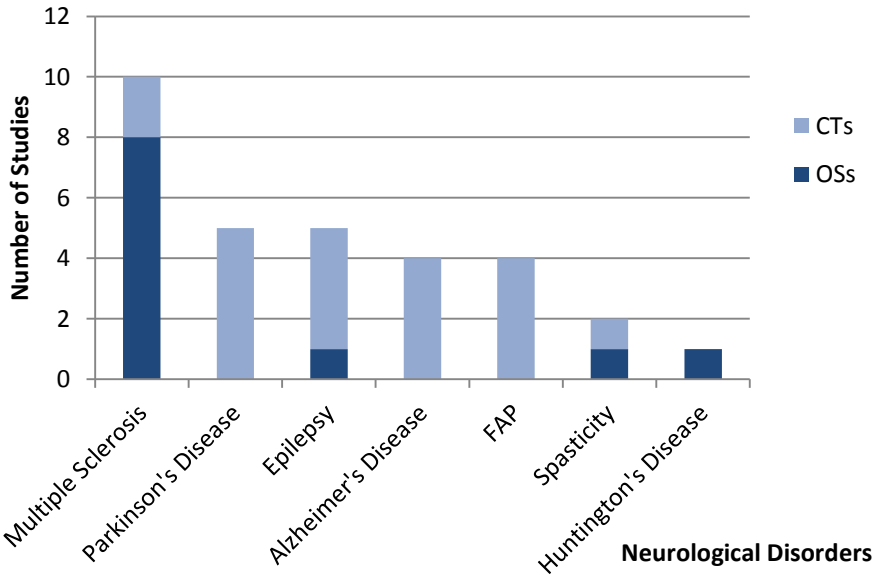

Figure 12 Number of Studies on-going in CIC by neurological disorders (2014)
(FAP: Familial Amyloid Polyneuropathy)

2.3 Centro Académico de Medicina de Lisboa

Centro Académico Médico de Lisboa, CAML, is a consortium that integrates the following institutions: CHLN, E.P.E. - HSM, FMUL and IMM. CIC is a part of IMM and is consequently a part

of this Consortium. The merge was signed on 8th December 2008 (2) and CAML has the objectives to: develop scientific, clinical and medical research; encourage innovation and education of medical research and health science; develop training programs; develop new therapeutic and diagnostic methods, such as rationalisation of resources; maximise the synergies arising from its geographical integration and high differentiation of human resources (14, 23).

CAML defends the importance to encourage and instruct academic population to develop new and better drugs and medical products (14). Therefore, the international cooperation for research and advance training in biomedicine and clinical medicine is one of CAML's main goals (23).

This consortium promotes clinical research and partnerships with the international research network, thus allowing the development of very innovative and complex projects.

Due to the diversity of stakeholders' expertise, the consortium can develop the design of CTs, conduct them, perform the interpretation of the data produced by CTs and develop other research studies.

The hospital is able to offer the clinical content, current proposal of research and complementary exams. IMM provides research expertise, access to labs and knowledge in basis science; and, additionally, the university offers knowledge, clinical training and desire to innovate. This way the proper conditions were created to encourage new qualified professionals to developed interest in clinical investigation (24).

All the previous conditions help the research and reduce the difficulties found by researchers, such as lack of resources, no time dedicated to research and the lack of methodological skills.

3. State of the Art of Clinical Research

This section presents an overview of the current Pharmaceutical R&D paradigm, an overview of the types of CTs, the position of Portugal in the conduction of CTs, the situation of CRUs as well as the establishment of clinical research networks.

3.1 Overview of Pharmaceutical R&D Process

Thanks to advances in science and technology, the pharmaceutical industry is entering a new and very promising development. At the moment, due to the high technological methods and knowledge the pharmaceutical industry has many potential prospects on the horizon. They are focused on developing a new era of medicines, the era of personalised medicines by harnessing the power of big data (25).

The industry has already contributed to a considerable improvement of people's health. A proof of that is the average of life expectancy. The European citizens can expect to live 30 years more than in the last century. Furthermore, the evolution of the pharmaceutical industry has allowed to live with a better quality of life (25). However, there are some diseases, including Alzheimer's, Multiple Sclerosis and orphan diseases that are still a big challenge to understand and produce innovative treatments.

Currently all new medicines introduced in the market are a result of a lengthy, costly and risky R&D process. The current pharmaceutical R&D process is considered unsustainable because the attrition rate has been increasing.

The expenditure has been rising due to the high cost with the scientific investigations, the conduction of the largest number of CTs required and with the high number of resources to reach the approval by regulatory authorities. Consequently, the time to conduct research and development of new drugs has been increasing too. Usually the development of new drugs, from the synthesis of the new active substance to their arrival on the market, takes about 12-13 years and costs about € 1,172 billion. Moreover on average, only one out of 10,000 investigational medicinal products (IMP) (Figure 13) will successfully pass all required stages of the research process to become a marketable medicine (25).

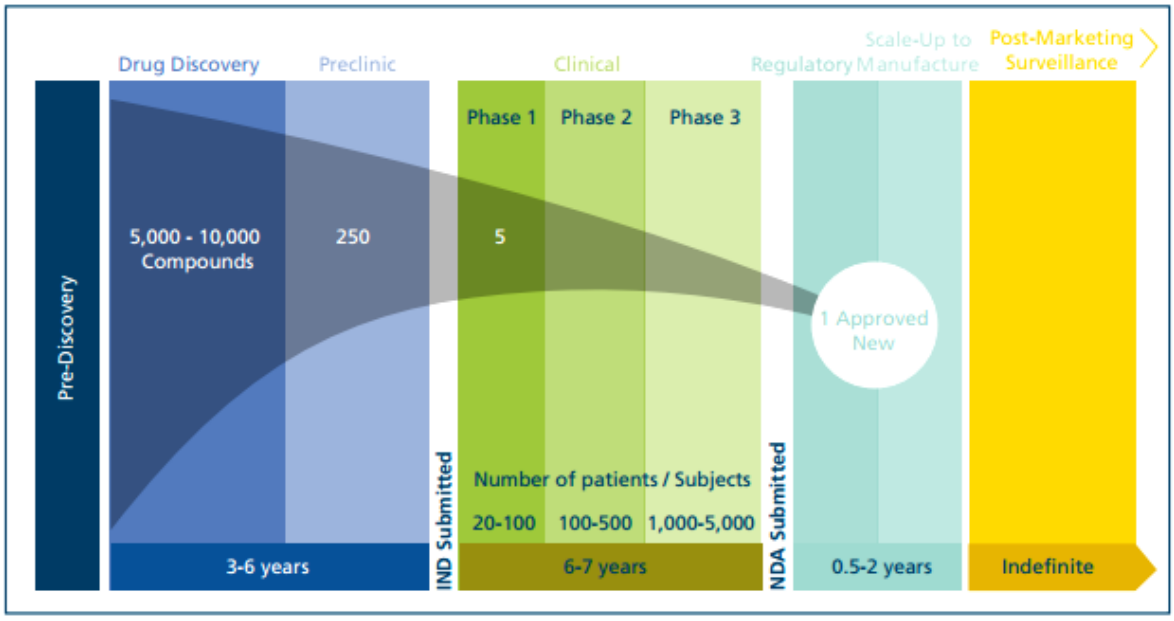

Figure 13 Pharmaceutical R&D Process (26)

After assessing these data the Pharmaceutical industry and competent authorities express the need to develop a new model of R&D of new drugs. In this context, a new concept of R&D emerges. This concept has the aim to obtain more information about the considered pathologies and their mechanism and only then should it be invested in the new molecule. To reach the necessary information the use of bioinformatics, a better evaluation of tools and knowledge management is indispensible (26).

This model allows an extensive knowledge of disease condition and consequently the mechanism of action of the new compound. Due to this, the process of research and development can carry on quicker and with more confidence (27).

In order to overcome the crisis a European initiative organised by the pharmaceutical industry and regulatory entities developed a strategy - the Innovative Medicines Initiative (IMI). Initially in 2008, when the strategy of IMI appeared, it was based on four pillars: safety, efficacy, knowledge management and education and training (28). Later, in 2011 the initiative was revised and seven areas of interest emerged: the patient as a focus of research; relation between disease and drug efficacy; knowledge and knowledge management; R&D strategies; drug development and regulatory framework; tools and techniques; and education and training (26).

In 2014 the IMI2 Agenda was published, where the major challenges in the European healthcare system, the pharmaceutical industry and the regulatory framework were discussed. The IMI2 Agenda focused on some strategies that provide the development of balanced projects with favourable characteristics to be successful. The strategy defends the union of all sectors of

healthcare ecosystem (i.e. healthcare practitioners, regulators, patients and payers to ensure new scientific advances) in order to deliver the right treatment to the right patient at the right time. IMI2 will provide tools, methods, and prevention and treatment options that will help to reach the vision of personalised medicine and prevention. The main goal is to develop a plan to initiate collaborative projects in order to overcome the bottlenecks in the healthcare system, and consequently offer an effective treatment to patients (29).

In this context, the IMI2 defined four major axes of research: target validation and biomarker research (efficacy and safety); adoption of innovative CT paradigms; innovative medicines; and patient tailored adherence programmes (29).

3.2 Clinical Research

Clinical research involves many different elements of scientific investigation and it is the main area responsible for developing knowledge in biomedical sciences (20). The basic research discovers the molecule but only the clinical research can transform it into a treatment (through drug development process). This type of research is about discovering the best treatment for patients using human subjects (healthy or unhealthy subjects) by an investigator.

During the journey of research and development the new molecule is submitted to many tests. Initially the compound is discovered due to the basic research, and then it is submitted to some animals tests (non-clinical studies) (30). After that the drug is tested in CTs and finally it receives approval to commercialisation (marketing authorisation) (30).

The research can be patient-oriented, epidemiological and behavioural studies or outcomes and health services (20). The patient-oriented research involves an individual person, a group of people or material from humans (it can be for example therapeutic interventions and CTs); the epidemiological research evaluates the distribution and behaviour of diseases, and the outcomes and health care services assess the health situation of the population to understand the most effective and efficient intervention, treatment or service (20, 31).

The clinical research helps to translate basic research into new therapeutics and data into benefit of patients (32). In fact, this process of research is characterizes from the lab step (experimental investigation) to the introduction to the consumer market and beyond (32).

Basic research is the first step of research, which is usually performed in research laboratories as opposed to the clinical research, which is later carried out in hospitals or health units by qualified health professionals (33, 34).

When a new compound is discovered, pharmaceutical companies begin some laboratory and animal studies to understand if the compounds have some activity in the targeted disease, to assess the characteristics of the compound and to plan the development. If the molecule shows some positive evidences the pharmaceutical companies move forward to CTs (35, 36).

CTs are studies performed in human subjects with the intention to discover or verify the effects of one or more investigational medicines, device or biologic product (37, 38). A detailed description about CTs classification is presented below (see 3.1).

The whole process is regulated by competent authorities that evaluate the protocol, verify the compliance with GCP's, ensure the quality of the investigational product, ensure subjects' rights, well-being and safety during a research and also ensure that the results of CTs are credible (37).

3.3 Clinical Trials

Before carrying out any CT, the compound is submitted to extensive investigation and only when the results of non-clinical investigations indicate that the drug is acceptably safe for the human investigation can the researchers proceed to the next step, the CTs (19).

According to the ICH, CT is "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" (16).

The clinical development is a step before marketing authorisation and where the investigators do several tests to evaluate the safety and efficacy regarding the establishment of parameters such as toxicity, potency, dose-finding and other conditions. To acquire marketing authorisation this step is essential because the pharmaceutical company has to show a document full of information about therapeutic indications, routes of administration, dosages, targeted population, expected effects, interactions and safety data (such as precautions and contra-indications). The whole process usually takes about 13 years, which is long, according to the

current model of R&D process, but it is an indispensable journey because there are many things to understand and study. However, the pharmaceutical industry has been searching for an alternative clinical development process with the objective of reducing the attrition rate and optimising the resources.

As stated in the ICH-E8, the CTs can be classified either according to the temporal phases or according to objectives (Figure 14) (19). Until now the division of the CTs has been according to four temporal phases (from Phase I to IV). The type and design of studies performed in each phases were determined according to the results of previous phases. Due to the paradigm of R&D process and the evolution of CTs this concept is no longer accurate. The same type of CT may occur in different temporal phases of the CT development. Sometimes "the phase of development provides an inadequate basis for classification of CTs because one type of trial may occur in several phases" (19). Thus, the classification through objectives of study is preferable because it is more reliable. Despite this fact, the classification according to temporal phases remains more used than types of studies (19, 26).

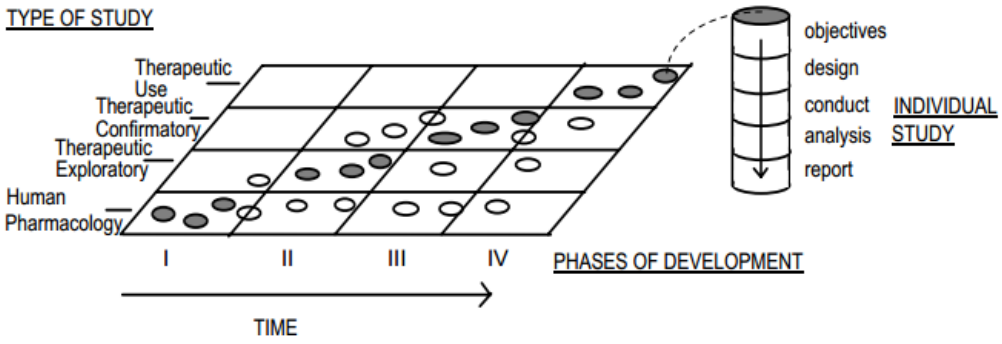

Figure 14 Correlation between phases of development and types of studies (by ICH-E8) (19)

Specifically, there are 4 temporal phases of development and regarding to the most typical kind of studies performed the classification of CTs are divided into:

- Phase I *(Human Pharmacology)*: This phase is characterised by the initial administration of an investigational new drug into human. The studies do not have any therapeutic objective and the patients are usually healthy volunteer subjects.

The objectives of these studies are: the estimation of initial safety and tolerability; the investigation of pharmacokinetics; and the assessment of pharmacodynamics (Early measurement of drug activity) (19).

- Phase II (*Therapeutic Exploratory*): These studies intend to explore therapeutic efficacy in patients. It is conducted in a group of patients with narrow criteria and closely monitored. An important objective for this step is to determine the doses and regimes to Phase III. Additional objectives of CTs in this phase may include evaluation of potential study endpoints, therapeutic regimes and target populations (dose-response relationship, increase the knowledge about efficacy, safety and tolerability) (19).

- Phase III (*Therapeutic Confirmatory*): In this phase the primary objective is to demonstrate, or confirm therapeutic benefit. These studies are usually developed to confirm the preliminary evidence in phase II. These studies provide an adequate basis for marketing approval. Moreover, it may also further explore the dose-response relationship, the action in different stages of disease, or combination with other drugs (assessment of benefit-risk). In some cases it also studies the influence in extended exposure. In conclusion, these studies are responsible for completing the information needed to support the official use (19).

- Phase IV (*Therapeutic Use*): All studies are performed after drug approval and are related to the approved indication. These studies are important for optimising the use of drug and identify less common AEs. Through these studies it is possible to collect additional information about drug-drug interaction, dose-response or safety (19).

3.3.1 Clinical Trials in Portugal

According to studies performed by EUROSTAT, the pharmaceutical industry is one of the sectors in the global context which invests more resources in R&D (25). Despite the effort of investment, during the last years this investment has not been a synonym of an increase of success rate. Over the past 5 years the number of new molecular entities approved by FDA dropped 50%. Regarding Europe, EFPIA verified, as expected, a continuous decrease of competitiveness and a lower number of compounds produced throughout the last years (25).

In 2011, according to EFPIA report, the pharmaceutical industry invested in Portugal about €78 million. Most CTs conducted in Portugal are promoted by international pharmaceutical companies of R&D (in 2010 the international investment was about 94%). Despite the fact that Portugal has an excellent scientific capacity as well as qualified professionals, the number of CTs performed in the Portuguese territory has declined in the last years. APIFARMA and

PricewaterhouseCoopers have developed some studies that pointed Portugal as one of the countries that has the lowest number of CTs submission in Europe. When the time of approval process of new CTs is evaluated, the average time of approval exceeds 70 days (period between submission of request for initial approval and reception of approval by last regulator). These data represent a progressive loss of competitiveness and this fact is really worrying.

An APIFARMA project conducted in 2009 where Portugal was compared with other European countries with similar conditions showed that Portugal was the country with lowest active CTs, lowest number of sites, lowest number of recruited subjects and consequently the country with smallest investment in clinical research. Regarding the CTs submission in Portugal, between 2006 and 2012 a decrease of 26% was verified (in 2006 160 CTs were submitted in Portugal, and in 2012 only 118 CTs) (Figure 15) and the number of subjects recruited in CTs per million of inhabitants was among the lowest in Western Europe, reflecting lower access of innovative therapies. (27, 39, 40)

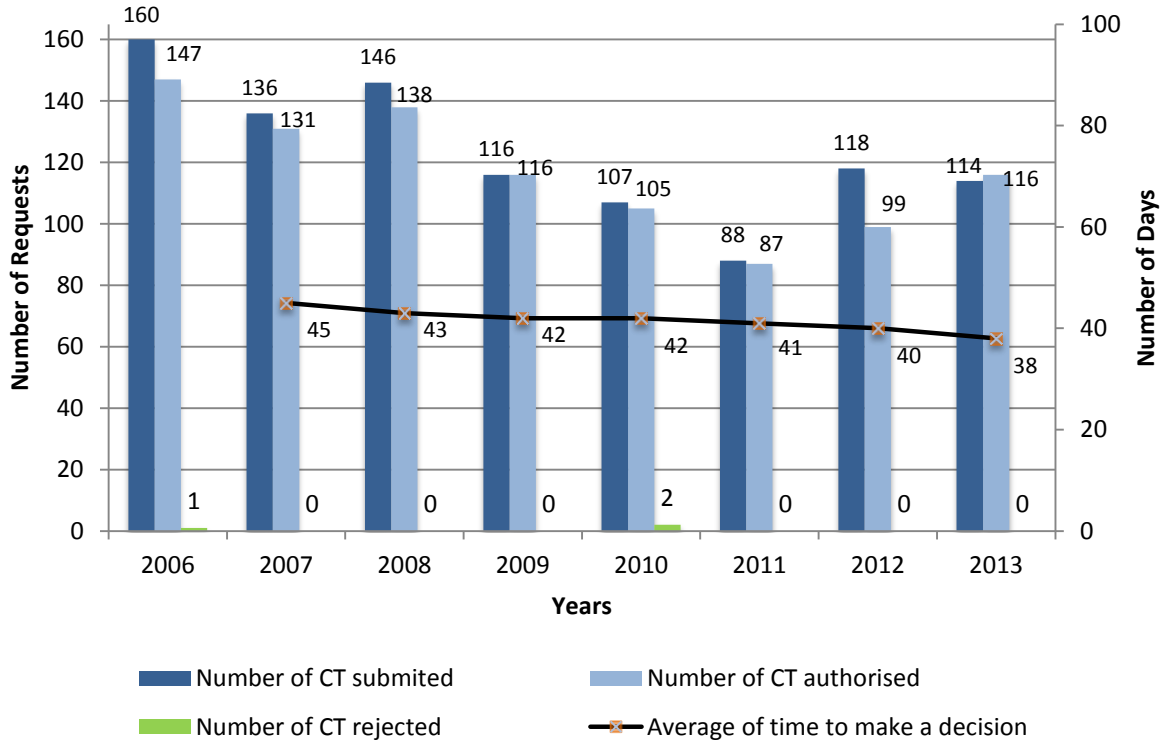

Figure 15 Number of Portuguese CTs submitted, approved and rejected with respective time of decision (2006-2013) adapted from PriceHouseWaterCoopers (27, 40)

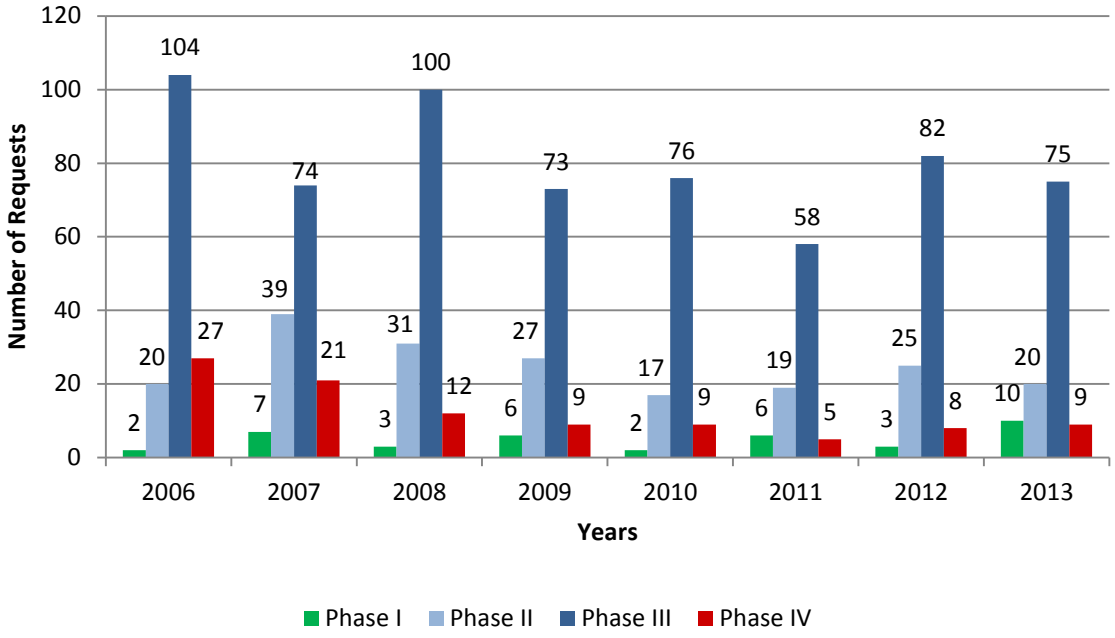

Figure 16 Number of CTs performed in Portugal by phases (2006-2013) adapted from PriceHouseWaterCoopers (27, 40)

Regarding the recruitment rate, Portugal, it was only able to recruit 70% of subjects initially planned (based analysis between 2007 and 2011). Thus, it was classified as one of the countries with least potential to conduct clinical research.

Due to national conditions most CTs conducted in Portugal are in phase III. Phase I of CTs has almost no representation. (Figure 16)

This reality is a result of the lack of investment in clinical research. The entities with capacity to invest in science and technology, for example FCT, have prioritised the basic/laboratory research. It is urgent to change this tendency and contribute for a culture of clinical research. The investment in this area allows completing the cycle of innovation and following the compounds from basic research to commercialisation (41). Therefore, clinical research is a crucial link in the cycle of biomedical innovation and profitability of the initial investment, encourages a culture of rigour and quality control in health care, increases the skills of health professionals, raises the rate of employment, allows patient access to innovative therapeutics, enables the adoption of best practice in following-up the patients and contributes as a source of alternative funding. According to 2012 APIFARMA assessment, the activity of CTs in Portugal produced a gross value added of €72M, a public saving of €3,5 and created more than 1000 jobs (42). After a general evaluation many factors indicate that Portugal has suffered progressive loss.

Several obstacles and barriers which hinder the development of clinical research were identified and then organised in 5 main categories: Policy and Strategy; Regulations Affairs; Organisation and Infra-structures; Incentive, Training and Career; Technology and Information.

In order to overcome these difficulties some action plans must be created such as:

- National strategy for clinical research;
- review of current legislation of CTs approval processes;
- best response of the national regulatory authorities;
- creation of specific legislation to disseminate CTs;
- creation of management structures for research;
- development of required conditions for clinical research conduction (academia and pharmaceutical industry);
- professionalisation of support structures to conduct activities with rigour and excellence;
- creation of sites of excellence;
- incentives, training and career development in clinical research;
- encouragement of research partnerships.

After national authorities had realised the importance of clinical research some strategies were implemented with the objectives of recovering the efficiency and promoting the dynamics of clinical research, such as the integration of Portugal into clinical research networks (for example ECRIN – European Clinical Research Infrastructure Network) and the creation of a national consortium - CRIN (Portuguese Clinical Research Infrastructure Network) which has the aim to attract European funding for academic CTs. This action allows Portugal to develop some skills to ensure a good relationship between quality/costs and become more attractive internationally.

With regard to the time required for approval of CTs, identified by APIFARMA as too long, it has been verified a declining of approval time. The entities have been struggling to reduce the approval time. The average time for an opinion by the Ethics Committee for CTs was 59.7 days in 2011 and 42.3 days in 2012. For an opinion on substantial change it took 34.4 days in 2011 and 30.1 in 2012 (39).

3.4 Clinical Research Unit

A CRU is a unit specialised in developing medical research. In this type of research unit the CTs are the main types of studies conducted but not the only research activity (20).

This structure dedicates itself to coordinate clinical research; and analyse of CTs, non-interventional studies (epidemiologic studies and OSs) and health services research (diagnostic methods). Some CRUs accept any type of study whereas others only focus on specific medical areas, type of study or specific phases (20).

Doing clinical research requires the active participation of patients and several health professionals.

The CRU should comprise a multidisciplinary team that includes investigators, coordinators, nurses, pharmacists, administrative professionals and health technicians. Additionally there are also administrative professionals, pharmaceutical professionals and a laboratory technician responsible for the assessment of biological samples results.

The CRU is characterised as a space where the clinical investigator develops research (20). It can be in a public or private health department, a lab or other entity with adequate resources (material and human) for conducting CTs. The space can be a hospital or another health unit that ensures the requirements of enrolment, assessment, data registration and the follow-up of the subjects. The academic structures usually offer the requirements to conduct these projects easily. However, this does not mean that their execution should be limited to these institutions (43). The characteristics of the space depend on the type of study and design, the protocol, the knowledge of the clinical area, statistical analysis of the biomedical information and if there are protocols with external structures in specific domains (for example physiopathology, neuro-image, psychology). For example sometimes the primary care health units can be the most appropriate choice while other times they can be unadjusted (20, 43).

Nevertheless, in any place the clinical research must be carried out according to the GCP's. This guideline defines how CTs must be conducted, and the roles and responsibilities that all stakeholders have to respect. The main objective of these rules is to ensure the human rights, safety and well-being of subjects, according to Helsinki Declaration. In this context, the subject safety demand and the quality of the produced data arise. Thus, it is necessary to make the sites where the study will be carried out adequate (16).

The main objective of the CRU is to offer to a medical community the favourable and necessary logistic structures to develop high quality clinical research. (20)

In the CT case, there must be rooms for: the assessment of subjects; coordination work room; a room for some interventional procedures; archive room to keep data for long term; and a room to monitor and preserve the CTs data of the active subjects'. Additionally, there should be a unit to shorten the duration of admission, a room to process the biologic samples, an area to storage the biological sample (capacity for maintaining the samples in cold temperatures) and drugs (with controlled temperatures).

All these requirements guarantee that the CRU has the necessary conditions to conducted clinical research; improve clinical knowledge; and improve team research efficiency, thus facilitating the organisation of the institution.

Officially, in Portugal, there are no national politics to implement CRU or to conduct clinical research (20). However some hospitals develop CRUs and some internal guidelines with the intention to overcome the lack of standardisation and regulation regarding clinical research. For example CIC-CAML, IPO-Porto (44), AIBILI (45).

These units have many advantages but the principal benefit is the possibility of helping the investigators to carry out their research, whose logistic requirement is incompatible with their routine. The main factor for professionals to refuse investigation in Portugal is the lack of available time and specialised training. Thus, the implementation of CRUs could be a solution to encourage the health professionals to do some research (20, 46-49).

Evaluating from a more theoretical perspective, there are more benefits with the existence of specialised research units, such as improving the conduction of CTs; allowing scientific consultant activities (type of design, writing scientific protocols, data bases, statistical analysis); promoting specialised training in clinical research; and encouraging other professionals (no physicians) to do some research (20).

Through the implementation of these services the Portuguese institutions will be more recognise; the Portuguese groups of research will be more efficient; the conditions will become more attractive for new research groups and basic research and clinical research in ambulatory can be bridged (20).

3.5 Clinical Research Networks

The current R&D process is responsible for discovering innovative treatments; however, nowadays, the system is inefficient because it is very expensive, slow and expresses a high

attrition rate in drug discovery up to approval (26). The increasing expenditure in the biopharmaceutical market combined with a slowdown of innovative medical therapies reaching patients is an evidenced problem of the R&D paradigm. Presently the pharmaceutical industry is facing a crisis and in order to overcome this situation it is necessary to assess the causes of the problems and search for a different way that can be profitable (improving the productivity and cost-efficiency) (26). Bearing this objective in mind, some promising ideas have been emerging, such as the establishment of a research network and partnerships. These concepts consist in a synergic relationship between two or more entities/groups that gather in order to carry out an activity, with each part contributing with resources to reach a common objective. The demands for funding and efficiency leave no alternatives to collaboration between research institutions.

Some regulatory and pharmaceutical authorities have hardly thought about "how" to change the R&D model. Unfortunately this issue is always a hard one because the model is very complex and there are many stakeholders involved, such as the pharmaceutical industry and its liabilities to shareholders, regulatory entities, patients and general public (50). Although it is very complicated to draw a new model, the experts have assessed the paradigm, detected the probable causes of failure and indicated some possible ways to counter the tendency and to update the model according to the new reality.

Some problems begin immediately in the regulatory level because there is overregulation and rigorous methodology, which makes studies expensive and the return lower (higher costs generated) (34, 46). Furthermore, other difficulties emerge in the practical field, specifically in CRUs. They include small number of health professionals with expertise in pharmaceutical R&D process, and a lack of support and resources. In addition, a slow recruitment was verified due in part to service pressures on practitioners (46-49). Fortunately, the intervention needed here seems easier than in the regulatory level.

Hence, in this timeline solutions are expressly needed to innovate the biomedical market and produce high-quality products in due time. For these problems experts suggest the CRUs to join forces and work on the same projects together (15). Setting up a partnership between entities and establishing Clinical Research Networks seems like a way to increase success rate, because there are more resources and knowledge together for the same project. Clearly, the main advantage of this strategy is bringing together all those interested in funding, pursuing and using research. In addition, the access to a specialised staff of research, opportunities for professional development, and the support of senior researchers seems to be highly relevant to promote success (15).

The main objectives of a multicenter program are to conduct research which is quicker in introducing the investigational product into the market; investigate the safety and effectiveness of current therapies; support the delivery of high quality research; collect data; and disseminate the clinical findings to the healthcare community and public. In this way, it is possible to assess the therapies in CTs and reducing the delay in developing new and effective therapies (31, 32, 49, 51).

The establishment of Clinical Research Networks enables researchers to be connected in spite of being physically separated, and thus they can share their experience, expertise, resources and exchange valuable skills (15). They make up a single, more diversified, complete and stronger team. All these characteristics are favourable to achieve success.

Furthermore, this practice can be a way to encourage greater engagement of biomedical population in research. In addition to patients, the health professionals also need to be persuaded and trained to understand the benefits of participating in and conducting CTs (34, 46, 52, 53). It is therefore necessary to build a culture of clinical researchers (39).

In the context of already established clinical groups, it is to underline that there are still some aspects about how to comply with the target number of recruitment that has potential to improve (54). A possible strategy to overcome this problem could be involving and training new researchers and refreshing the established groups (47). Despite the high levels of investment, many studies fail to recruit their target numbers (47). Recruitment for CTs is a complex task and can be influenced by many factors (49). The CRUs still find many difficulties in complying with the time period for recruiting the number of patients set out to be included. Clearly, this difficulty undermines the whole conduction of the study, as it implies an extension of recruitment time and, as a consequence, a study delay. Additionally, the delay may become a threat for the validity of the findings and increase research costs (47).

In 2009, out of a total of 114 UK trials, only 31% met their recruitment target, 45% recruited fewer than 80% of their target, and 54% of the trials required extension (47). Regarding recruitment, the creation of Clinical Research Networks makes it easier for the patient to participate in clinical research (49). By increasing the number of participants, it is possible to reduce the time of recruitment and optimise the research activity.

In case of rare diseases, i.e, diseases or conditions that affect less than 200,000 people in the United States (55) or less than 5 in 10,000 in European Union countries (54), recruitment becomes even more difficult than usual, because there are less potential participants. However, if

a network is created for those diseases, the enrolment of subjects becomes easier and quicker (56).

Another example of advantages can be the fact that in some diseases the target population is spread across a huge geographical area and in that case the research networks allow access to a large and diverse number of patient population for CT research – decentralization of CRUs and centralisation of data (15).

According to results published in 2012 regarding a research network in Sweden, the creation of networks facilitated recruitment and made it possible to collect and share data from a larger number of patients. Furthermore, after the collection of patients', it is saved in a database, allowing later an identification of potential research participants for other studies (57). It would be expected that one consequence of this activity could be the establishment of banks of medical and biological materials for the community (58). Thus, the units together can generate a lot of new knowledge, much more than a single research unit.

4. On the Job Training

This section includes the description of the general training that I received during the 10 months of traineeship and the specific training related to coordination of CTs and Oss, data entry, co-monitoring, pharmacovigilance and medical writing.

When I arrived at CIC I received a generic training about clinical research routines activities, and only after that was I qualified to initiate activities related to coordination of CTs, OSs and other unit duties.

The generic training provided by CIC allowed me to be familiar with the activities of the institution and become able to perform an efficient work. The specific training consists in the activities developed during the training. The specific training was more focussed on study coordination but also covered other subjects related to clinical research, such as co-monitoring, pharmacovigilance and medical writing.

Figure 17 schematically represents the chronogram of the different activities performed during the generic and specific training, which will be described below.

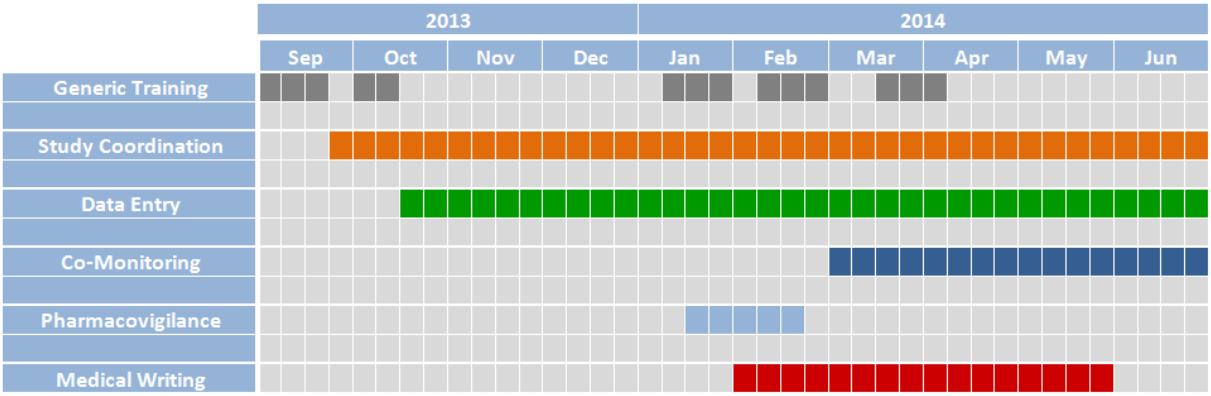

Figure 17 Timeline with the activities developed during the training

4.1 Generic Training

This section describes the formative sessions and workshops that allowed me to participate actively in the activities of CIC. Some sessions were held by members of CIC but others by external people.

4.1.1 Training about the Host Institution

When I arrived at CIC I was introduced by SCs to the history, organisation and infrastructure of the host institution. Additionally, I searched a little more to know about its mission and objectives.

The unit was opened in 1999, and around 2002/2003 the group experienced its first expansion and established new collaborations. Since then, the group has provided facilities for submission, logistic work and conducted CTs in new neurologic research areas. In July 2013, other logistic changes occurred and Professor Doutor Joaquim Ferreira became the principal head of CIC.

After this presentation, CIC routine and its procedures, the protocols of on-going studies and the team were enunciated. After this session I became able to work with the SCs in their activities, with the investigators and other staff. This period was very important because it allowed me to understand how and why the procedures were carried out, how the infrastructure of the unit was, and to meet the people that I would work with.

Thanks to the organisation of CIC I could easily integrate into the routine activities, understand the timing of activities and the roles of function. I also had to understand the CHLN, E.P.E. - HSM and IMM standard procedures to CIC, since there is some information and requests that CIC has to comply with.

4.1.2 Clinical Research Team Hierarchy

During the first weeks I was given an overview of the hierarchical structure of CIC. Consequently the importance of a good organisation of a clinical research group was stressed. There are many intervenients in a research team and their activities should be clearly defined before initiate any activity (18). Thus, before doing any activity, the SCs at CIC identified the members of all on-going studies and their roles. I also was reminded of the type of members that should make a part of a clinical research group: PI, Co-investigators, SC, Pharmacists, Laboratory Technician and Study nurse, and their roles are:

- The PI is the primary responsible for the conduction of the CTs on site; for ensuring the performance of the procedures according to the protocol; and for guaranteeing the training of the group and verifying if the elements are able to carry out the procedures.

- The Co-investigators have expertise in CTs conduction. They usually: recruit subjects; provide medical care to the subjects; ensure the rights, safety and well-being of the participants during the CT; prescribe the investigational medications; and, if applicable, withdraw participants from the study.

- The SCs are responsible for all logistic management. It is their function to: schedule the patient's visits; help the investigators; prepare monitoring visits and assist the monitors. They also organise the complementary exams according to the protocol visits, guide the subjects and clarify them about any doubt that may arise. The SCs can also help in several procedures during the clinical visits, such as measuring the vital signs, perform electrocardiograms (ECGs), and process and send the biologic samples to the central team. The SCs work with monitors, patients, investigators and the central group.

- The pharmacists are responsible for receiving, storing and dispensing the IMPs according to the protocol. In the case of CIC, the prescription can be performed by Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). After the investigator allows the dispensing of IMP, the prescription can be sent to the pharmacy by email or fax and after that the pharmacy assistant brings the IMP to the site. After the investigator verifies the batch number and IVRS/IWRS number, the IMP is delivered to the subject.

- The Laboratory Technician and Study Nurse are responsible for collecting biological samples. The Study Nurse also performs some invasive procedures according to the protocol.

4.1.3 National and International Laws

SCs have to know extensively the main national and international laws about the conduction of CTs. During the Master's Degree and Undergraduate's Degree I received some training regarding on such laws, and when I arrived at CIC, these issues were also addressed. It

was stressed that the main concern of the site is not to violate the confidentially, rights, safety and well-being issues. So, the following documents had to be considered:

- ICH-GCP: Good Clinical Practices (16) is a guideline about ethics and scientific quality standard data for CTs. This guideline is essential to ensure the protection of subjects and the production of accurate data.

- Helsinki Declaration – Ethical principles for Medical Research involving Human Subjects adopted by 18th WMA General Assembly, Helsinki, Finland, June 1964 and last amended in 2013, is a set of ethical principles developed by the World Medical Association that guides a human research. I have also considered this document because our work involved human subjects.

- Directive 2001/20/CE April 4th (59), defines GCP's for conducting CTs with medicines for human use. It was transposed to Decree-Law 46/2004 of August 19th(60), now Decree-law 21/2014 of 16th April (61) (updated version), to be enforced after June 2014.

- Directive 2005/28/CE (62), which establishes the principles and detailed guidelines in GCP's with medicines for human use. It was also transposed into a national law, the Decree-law 102/2007 of April 2nd (63).

- Proposal for a Regulation of the European parliament and of the council on clinical CTs on medicinal products for human use, and repealing Directive 2001/20/EC: on 17 July 2012 the European Commission adopted this proposal, which introduced some amendments in relation to Directive 2001/20/EC (59) and 2005/28/EC (62). The proposal aims to rectify some inconsistencies verified in Directive 2001/20/EC (64).

- Directive 95/46/CE October 24th (65): this directive is about the protection of subjects with regard to the processing of personal data and the free movement of such data. That was transposed into national law: Decree-law 67/98, October 26th (66). I had to use these laws whenever I was in contact with the subjects' personal

data and when I had to explain to the participants that their data was protected and only the competent person had access to them.

4.1.4 Good Clinical Practices Training – ICH-GCP's Guidelines

Being compliant with ICH-GCP's is the principal requirement for people who work in clinical research. Therefore, I attended a Good Clinical (Trial) Practice Training at the Universidade de Aveiro, on 1st October 2013, which allowed me to strengthen my knowledge about this issue.

4.1.5 Monitoring Training

To complement my training and due to my activities as a co-monitor in the OS – European Huntington's Disease Network (EHDN), I attended (27th March) two days of a workshop about monitoring CTs and OSs organised by Forpoint ©, a branch of the Clinical Research Organisation – Keypoint ©.

After this workshop about monitoring data, I was trained by a SC to supervise and assess data from the database of EHDN, and monitor and launch queries, if applicable.

4.1.6 Training about on-going studies at CIC

I was instructed by SCs of CIC about the protocol of all on-going studies, visits and procedures. Additionally, I learned to archive study documents in the investigator site file (ISF).

Only after that did I become able to collaborate in CIC activities.

4.1.7 How to prepare an audit

During my training CIC was submitted to an external audit from 28th – 30th April. To participate in this activity I had to learn some concepts very well, such as: what an audit is, what types of audit exist, how to prepare the sites for an audit and the objectives of that action. So, in order to become able to participate, I had to study the theme on my own and additionally the SCs taught me the requirements and organisation of the audits.

4.1.8 Training in technical equipment for clinical studies

During the period of training I had the opportunity to deal with different situations and perform several activities. The SCs taught everything they knew about daily activities of a CRU.

One of these activities was related to laboratory procedures of each CT. I received training by the SCs to process, store and ship the biological samples. They explained how to handle different laboratory kits. Specifically, I learned that initially it is necessary to identify the correct laboratory kit and write the number of the patient on the tubes; then help the laboratory technician/study nurse to collect the samples; and finally process them. Some samples need to be centrifuged, and in this case it is essential to know the right programme and follow the indications of each study. After that the samples must be stored and/or shipped.

The SCs were also responsible for performing ECGs in patients. Hence, I received instructions to deal with the electrocardiograph. I learned how to perform ECGs and manage the electrocardiograph. In the beginning of my training, the SCs taught me how to introduce the patient's identification; place the electrodes correctly; print the result; and send the exam to the central team.

The collection of vital signs was also an activity of the SC. In consequence, I was also trained to perform do measurement of vital signs. In most visits, vital signs are collected, such as: the blood pressure, pulse, respiratory rate, temperature, and weight. The height is also recorded for all CTs.

4.1.9 Training in software tools from clinical studies

Currently the use of high technology materials for the collection of data is usual and our unit was an example of this fact. Thus, additionally I had to manage some equipment and technological devices, such as, iPads, laptop, electronic pens and interactive platforms. Obviously these components made the conduction of studies easier and the collection of data more accurate. To know how to manage them I had to receive training by SCs and online courses. They taught me to have access to case report form (CRF) and data entry; and to validate, correct and answer queries, according to GCP's.

CIC had several studies, with different types of CRF platforms. Most CRF were electronic case report form (eCRF), only one was in paper. I could work with the following electronic systems: Inform ™, Viamec ™, Viedoc ™, QCAT ™, Medidata Rave ™ and Oracle ™.

Some CTs had specific online databases platforms (such as QCAT™) where patients' data were introduced, for example, psychological and neurological scales. So that I could become able to participate in these tasks the SCs explained me the principles and I also read the instruction about them.

In addition, I received training about the systems responsible for the IMP allocation and prescription. Some CTs had IVRS and other IWRS, and the SCs taught me how to use both.

In order to obtain a specific training to be able to start collaborating in new CTs all members of the group must do some training about GCP's whenever a new CT starts (requirement of almost sponsors). I also did some of these GCP's trainings.

Due to my activity related to data entry, the statistics technician taught me how to work with SPSS, and only after the explanation did I became able to help the technician with the database.

4.2 Specific Training

In this subsection I will describe the specific experience acquired during the training and all the activities performed, firstly as a SC, then as a data entry technician and co-monitor of OS and finally as a writer of a paper. These activities involved many stakeholders, and thus to ensure the confidentiality of all data, safety, rights and well-being of patients I had to consider some guidelines, directives and laws. I always had to follow them because that is a requirement of regulatory authorities and I was generated CT data that are intended to be submitted to regulatory authorities.

4.2.1 Activities as a Study Coordinator - CTs and OSs Coordination

This was the main activity of my training. During the 10 months of training I was able to experience several stages of CTs and OSs. At the end of my training in CIC around 31 studies (20 CTs and 11 OSs) were being conducted (Figure 10). During my training some studies were

initiated after my training began, others were completed during the training, and others were finished earlier.

To sum up, during the period of training the CIC initiated 6 CTS and 3 OSs, responded to 3 feasibility questionnaires and concluded 5 CTs (unfortunately two of them suffered an earlier termination without any subject recruited).

After the generic training I was able to work in any study of CIC. However, to facilitate the work in CIC I was allocated to specific CIC studies, and due to this reason I worked full time with Alzheimer's Disease.

I had the opportunity to follow one of the CTs since the SIV; due to this reason I can say that this was the CT where I had more activity. It was denominated as EPOCH (An efficacy and safety trial of MK-8931 in Mild to Moderate Alzheimer's Disease (P07738)). This CT is a phase II/III, multicenter, randomised, placebo controlled, parallel-group, double-blind efficacy and safety trial of MK-8931 with a long term double-blind extension in subjects with mild to moderate Alzheimer's Disease (Protocol No MK-8931-017-08) sponsored by Merck Sharp & Dohme Corp. (67). Approximately 1960 participants, aged 55-85 of both genders, with diagnosis of probable Alzheimer's Disease mild to moderate severity (according to some scales) would be randomised, either with MK-8931 or placebo (67).

The CT has two parts. The purpose of Part I is to assess the efficacy and safety of MK-8931 compared with placebo administered for 78 weeks in the treatment of Alzheimer's Disease. Part II is a long term double-blind extension to assess efficacy and safety of MK-8931 administered for up to additional 260 weeks. Additionally, there are two sub-studies (67).

This CT is very complex and the first evidence of this is the design of the study, the second one is the large number of procedures to carry out in each visit and the requirement of the participation of several people and departments. To ensure the correct application of the procedures I had to create checklists with the activities for each visit and the order of its application required by protocol. In this CT the main data is extracted though scale, and due to this reason the sponsor was very meticulous in the collection of this information; thus we had to manage several technology tools to ensure the accurate and quality of the data. Because of that I had to create a guide document with instructions to use the tools and in every visit I had to remind the investigators of how use the technology properly.

In addition to the coordination of dementia CTs, I helped my colleagues to coordinate the other studies, when needed.

The SC has a central position in the clinical research site, being responsible for following the studies in all their stages. The SC must work with all members of the research group: monitors; sponsor/CRO; international group; subjects; administration board and ethics committee.

Thus, as a SC I could participate in a wide variety of activities. I could help with feasibility activities; Site Initiation Visits (SIVs); preparation of regular visits; monitoring of visits; close-out of visits; archiving of documents and in an audit of an on-going CT. In some of these activities I had an active participation but others I only provided some support.

During the 10 months of training I participated in coordination activities of 17 CTs, however, my main activity was in Alzheimer's Disease and dementia CTs (that represented 3 CTs of CIC studies).

4.2.1.1 Feasibility phase

The feasibility is a pre-CT phase in which the sponsor contacts and asks the PIs about their interest in conducting the CT; then a feasibility questionnaire is delivered; and after this the PI and SCs scheduled a meeting to fill it in. The procedure of feasibility allows choosing the potential sites and s.

This questionnaire has the objective of evaluating the clinical research site conditions and PI availability; and providing the main characteristics, challenges and requirement of the CT for the research group. When the PI has interest in conducting the CT, he or she must provide some specific information, which is usually data about the site experience in clinical research, the target disease, resources and facilities available, and who the person of contact is, in case of additional questions. After all this information is sent back, and the site waits for a feedback.

If the sponsor or CRO agree on the implementation of the CT at the site, the next step is a face-to-face feasibility visit. In this case, the meeting is between a representative of CRO/sponsor, PI and SC. During the meeting the PI signs the confidential agreement and then the study protocol is presented for the first time. It is at this time that the PI has the opportunity to give opinion, discuss the protocol and inclusion/exclusion criteria, and any other ambiguous issue. The following issues are discussed: the number of patients that should be recruited; the financial contract; and the approval timelines from the Administration Board of the CHLN, E.P.E. – HSM and the Ethics Committee.

During my training some feasibility meetings occurred in the unit. Although I did not participate actively in any, I provided some support in one of them. The SCs explained me that the feasibility meeting can be very different according to the sponsor/CRO. Therefore, if it is the first time that the sponsor/CRO contacts the site to conduct the CT, the meeting usually takes a little longer, because the SCs must guide the guests on a tour around the facilities. If the sponsor/CRO already had a past experience with the site, the visit can be quicker. In this scenario the site can just confirm the condition and resources by answering questions. In both cases the site is questioned about the necessary conditions, required facilities and available resources. In case the site needs any material it is requested to the sponsor or CRO to provide it.

The next step is the CT submission to the Administrative Board and Ethics Committee, the role of the SC in this step is to establish the connection between all intervenient.

Specifically the SC:

- should be the link between the Ethics Committee of CHLN, E.P.E. – HSM, sponsor/CRO and PI because the CT must be submitted to Ethics Committee of CHLN, E.P.E. - HSM, and after being approved, it should be reviewed by Sponsor/CRO and PI;
- should present the CT to the head of the Neurology Department and ask for an authorisation for conduction. This entity must approve and write a document with the decision;
- gives support to the PI because the PI must prepare a letter to the president of the Ethics Committee of the CHLN, E.P.E. – HSM requesting a review of the CT;
- reviews the financial contracts and delivers them to the administrator of the Neurology Department to be approved by AB;
- obtains the CVs signed and dated by everyone involved in the CT;
- delivers the CT file to the Ethics Committee;
- communicates the results to the PI, Sponsor/CRO and remaining group.

4.2.1.2 Investigator's meeting

The investigator's meetings are appointments where the members involved in the conduction of the study (such as CRA, PI, co-investigators, SC, health technicians, medical monitors, quality assurance and managers) receive training about GCP's, study protocol, required procedures, and how to correctly manage the equipment and software. This step is very important because it is an opportunity for members to ask questions and make comments about their study doubts; thus, it should not be underestimated. These concepts were explained me to me by SCs after their participation in the investigators' meetings. I did not attend any investigators' meeting because I was a trainee and only the principal SCs were authorised to participate.

4.2.1.3 Site Initiation Visit

The SIV is characterised by the implementation of the CT in the site. In this visit the condition of the site to conduct the CT, the experience of the research group and the access to the subjects are reviewed. All elements of a group are presented for the first time the CT and its procedures. The monitor usually visits the infrastructure of the site (such as pharmacy, lab and storing room) and verifies if any extra equipment is needed. The main preoccupation is to ensure the good condition of the pharmacy, and the equipment to process and store the biological samples.

During the visit the presence of the PI and SC is essential because there are some aspects that must be discussed, specifically:

- CT Protocol;
- CT Design;
- Inclusion and Exclusion Criteria;
- Inform Consent Form (ICF);
- Investigator's Brochure;
- Investigator Site File (ISF);
- Investigator Medicine Product (IMP);
- Case Report Form (CRF);
- Complementary Exams;

- Target Population;
- Sources Documents (SD);
- Possible AE's and SAE's;
- PI responsibilities;
- Delegation Log;
- Central Laboratory;
- Pharmacy conditions;
- Monitoring Requirements;

After this visit the site keeps with the main documents about the CT and officially it is ready to start with the recruitment of subjects.

I participated in some SIVs and during this activity I helped the CRA's with organising and archiving the documents; verifying the laboratory kits and other equipment (already at the site); and checking the conditions of the ECG machine and additional equipment involved in CT procedures. The IVRS/IWRS and electronic programs are also activated and their proper functioning as well as all online platforms/ databases are ensured.

Thus, at this moment, the site can start the recruitment period.

4.2.1.4 Preparing CT Visits

After the implementation of the CT, the SCs have the responsibility to save and organise the documents and the equipment in a space with restricted access. In addition, it is also necessary to organise the CT according to the study visits and procedures described in the CT protocol for the subjects.

A good preparation of CT visits is essential because there is a decrease in the probability of error, and anxiety of the team; and an increase in self-reliance. All information needed is in the CT protocol and outlined in a flowchart usually presented in the CT protocol.

Most visits require a very diversified evaluation, such as clinical evaluation, vital signs, psychology evaluations, blood and urine collection, ECG and questionnaires of quality of life. Obviously, there are several people involved in one single visit and because of that, a previous organisation is fundamental. Thus, before each patient's visit I always studied the visit plan and complementary exams including results, and the last and next visit, to have a general perception

of the patient's situation and to know what I needed to do. This procedure allowed us to organise the study visit and to avoid wasting time.

To better understand the differences between visits, some important issues will be explained below.

4.2.1.4.1 First Visit

For the first visit of the subject the investigator initially explains the study and delivers a copy of an ICF to the patient. This action gives the patient the opportunity to think better about the approach. After that, another contact is scheduled to know and discuss about the patient's decision. If the patient agrees to participate in the CT, the screening procedures are initiated.

4.2.1.4.2 Screening Visit and Baseline/Randomisation Visit

When the patient agrees to take part in the study, a screening visit is scheduled and if all happens as expected the patient does the baseline/randomisation and the study begins.

In this type of visit I supported the investigator in any doubt about ICF, protocol, amendments and informed the patients about our availability in helping them with any situation related to the CT.

The alteration of ICF throughout the time of conduction is common and when this happens we have to remind the investigator and ask him/her to inform the participants and ask them to sign and date the new amendment.

In order to ensure the favourable state of the subject in some CTs additional exams are required. Is this case between the screening visit and the baseline/randomisation visit, we had to schedule exams, organise the transportation and inform the participants. After that, when the complementary exams results were favourable we scheduled a baseline/randomisation visit and the subjects could start the CT. In the baseline/randomisation some auxiliary evaluations were carried out and the IMP was delivered. Additionally we explained to the subjects and their family/caregiver how to take it and the special precautions.

Sometimes the patient did not have the required condition to entry in the study (inclusion/exclusion criteria) and in these cases the participants were denominated as screening failure.

During my training I had the opportunity to participate in at least 20 screening visits, and 3 screening failures. I had an extensive experience in conducting screening/randomisation visits, and these are data I can precise for sure.

4.2.1.4.3 Regular Visits

The regular visits start with a contact with the subjects some days before the scheduled visits. Thus, in order to ensure the attendance of the subjects to the appointments some days before the visit we called to them.

Generally, to prepare a CT I looked at the flowchart and verified which procedure had to be performed, only after that did I collected the necessary documents and organise them. There are some documents (independent of the CT) that should be considered in all visits, such as inclusion/exclusion criteria and medication allowed and prohibited. These documents are the first to be selected when preparing a visit. Additionally, I prepared the patient´s medical record, IVRS/IWRS worksheets, lab kits and their requisition, vital signs record, pharmacy prescription, the worksheet to schedule the complementary exams (such as ophthalmological exams and magnetic resonance imaging, when applicable) and the requisition to order dry ice.

Due to the fact that my main activities during the training were within the SC context I created some worksheets, checklist and tables with the CT visits and the procedures per protocol for some studies I was involved in. The objective of this procedure was to ensure that the CT visit would run smoothly and without errors. This way I could provide some assistance to investigator during the CT visit and ensure a correct data collection.

This was also a preventive measure because some procedures require time of administration, collection and duration and throughout this procedure the order of the procedures is guaranteed and forgotten tasks are avoided. Usually these worksheets are also usually regarded source documents.

On the day of the visit the patient gave me the IMP; I counted the medication returned and verified the IMP compliance. Only after that the remaining of IMP was sent to the pharmacy. After this first contact the investigator observed the subject, assessed the subject situation and made complementary assessment.

There were some visits where a collection of biological samples, vital signs, ECG and administration of psychological scales were necessary. Consequently, in this case I had to support

the psychologists and the lab technician. I had to process the biological samples, store and ship them when applicable; register the vital signs; administrate the ECG; and send it to the central team.

Sometimes it happened that the patient suffered some AE's. In this case a more thorough assessment was required and only then did the investigator decide what should be done. In certain cases, when the condition was doubtful the PI contacted the CRA to discuss the condition with the sponsor. When the health situation was not favourable to continue in the CT, the PI advised the patient to leave the CT, and an early termination was performed. In case the patient conditions were good to continue in the CT, the investigator prescribed more medication and a next visit was scheduled.

Thus, the SCs completed the IVRS/IWRS and consequently the pharmacy dispensed the IMP. When the IMP arrived at the Department of Neurology the investigator registered the lot number and the ID number on the subject's process. In order to ensure the correct intake of IMP we reminded the subject of how to use the medication and to bring the packaging (the empty, unused and the packaging with medication) in the following visit.

After all this process, I verified the patient's expenditures and reimbursed the subject.

I cannot precise how many regular visits I conducted, but I can affirm that since I could participate in CIC activities I performed a large number of them. I could participate in almost all studies of the unit.

4.2.1.4.4 After the Visit

After the visit I reviewed the source documents, checked the consistency of the data, introduced them in the CRF and in some cases I had to upload a PDF file with the psychological scales. I also verified the SAE's, AE's reports and respective follow-up.

Finally I archived all the documents and material used in the patient's folder in the respective division in the archive room.

4.2.1.5 Some other CIC activities

In addition to the regular visits there are more activities of the SC's competence that I could perform throughout the training.

In order to ensure the respect of the requirements of the study protocol and not to perform any violation, the clinical monitor was always close to the research group. Therefore, the monitor was always available to clarify any unexpected doubts. In this way I was regularly in contact with the monitor by e-mail, telephone and sometimes face-to-face in order to clarify questions; resolve problems related to third parties involved; do the update of the amendments and new indications; resolve queries; and follow the SAE's/AE's.

I also had to be in touch with external clinicians, central group and company of transport. This situation was due to the fact that CRO/Sponsors made contracts with other entities to perform the complementary exams. I also archived documents and I performed some activities of quality management. Specifically in order to ensure the proper conditions of the material I verified the validation date of the material used, such as laboratory kits, and if anything was missing.

To ensure a good conduction of the patients' visits every Friday the SC organised a table of the patients' visits for the following week and then I transferred to a specific document and sent it to the pharmacist and nurses.

Complementary to the main activities I usually did the download of the temperature recorded by freezer temperature logs once a week.

According to the sponsor/CRO requirements all the equipment used during the CT must be calibrated at least once a year. I participated in this activity too. I made the first contact with the calibration company, I asked them to come to the hospital and then I assisted the technician visit in the unit.

4.2.1.6 Monitoring Visits

The monitoring visits consist in visits by the CRA/monitor at the site to verify the compliance of the CTs data collected. These visits intend to ensure the safety, rights and well-being of the participants as well as the quality of data and the compliance between procedures performed, CT protocol and required guidelines.

Firstly the CRA/monitor contacts the site (via email or telephone) to schedule the visit according to PI, co-investigators and SCs' availability. Only after finding a compatible date the monitor/CRA moves to the centre. This bureaucracy avoids misunderstanding and waste of time.

Days before the monitoring visit I organised all the data, completed CRF, resolved queries and reviewed if the pending issues from the last monitoring visits had been already answered.

When the monitor arrived at the centre, he verified all source documents and I helped him to read the patients' records and to find specific information. After this the monitor will meets the investigators and the SCs to clarify further doubts.

4.2.1.7 Close-out Visit

The close-out visit is a visit that occurs after the last visit – last patient. Thus, by this time the site has already the recruitment period finished and all patients have completed the last visit. All CRFs and documents must be updated and completed, i.e. all the data must be introduced and no queries must be open. At this moment the sponsor/CRA can close out the CT at the site.

During the training I had the opportunity to collaborate in activities like these (previously mentioned); I helped the group to respond to queries and update some documents. After that the essential study documents stayed at the site until new instruction of sponsor, usually the next step was the archiving of the CT documents in the archive department of CHLN, E.P.E. – HSM.

During the 10 months of training I could participate in 3 close-out visits.

4.2.1.8 Archiving documents

After the CT close-out visits, the essential document must be archived during a specific period according to national laws. The CIC respects the indication of ICH – GCP's and keeps the data for at least 15 years (16).

To initiate the archiving of essential documents we had to wait for a sponsor's authorisation. Only after this indication could we contact the central archive of CHLN, E.P.E. – HSM, store the documents in specific archive boxes and send them to the archive.

When we received the authorisation of the sponsor, as a SC, I contacted the responsible for the clinical archive, informed that we had documents to archive according to specific requirements and asked to allow the entry of the boxes. To facilitate the identification of the boxes we made labels with the name and number of CT protocol, PI identification, Sponsor identification, and when applicable the CRO address and contact.

Regarding the medical records of the patients we archived them in the central archive because after finishing the CT, the patients were considered outpatient clinics and they were assigned to any Neurology Physician in the CHLN, E.P.E. – HSM. Thus, these data were kept in the central archive of the hospital Neurology Department hospital appointments.

4.2.1.9 On-going CT audits

There are different types of audits and any study (CT and OS) may have one or more during its lifetime. While I was in CRU there was an external audit to a CT and consequently I could participate in another activity. The CT audited was on-going at the follow-up phase.

Before an audit, a previous preparation is fundamental; thus, the CT must be verified from the first visit – first patient to the last visit – last patient.

Initially CIC was informed about the audit; then they discussed about a possible date and finally the centre received an audit agenda with the possible audited topics. When CRU received the agenda, this was discussed among the team and then a work plan was developed to review all collected data.

As a SC I verified the source documents, ambiguous situations, reviewed SAE's/AE's, and studied the protocol and additional procedures.

During the audit the team was questioned about some issues and because of that I realised the importance of all members being present during the session.

During the final meeting the auditor presented the findings and discussed them with the PI and the remaining group. Thereafter, the centre received a report email with the inconsistencies. Furthermore, the centre evaluated the findings and developed some corrective and preventive actions.

4.2.1.10 Observational Studies

CIC also had many OSs, and as a SC, I had to guide these studies. Here my activities were similar to the ones in CTs but easier. The OS usually has fewer visits and they are less complex. In CIC the OSs required a collection of medical history, demography data and in one of them the collection of blood and urine samples as well.

I had the opportunity of organising the files of data and, the visits; collecting some data; shipping samples; and archiving data. After the visits I had to introduce the data in eCRF and resolve queries. During my training I had the possibility of helping in activities regarding the conduction of 6 OSs.

4.2.2 Data Entry

Due to this I developed some activities in a personal project of an investigator of CIC. The project was about Parkinson's Disease surgeries and I helped the statistics group to collect and introduce the data in a database to later work them and infer about the result of the surgical procedure in patients.

4.2.3 Co-Monitoring in a OS

Despite the fact that my main activities were performed as a SC I could do some co-monitor tasks because CIC was responsible for monitoring a prospective cohort study, a European OS, European Huntington's Disease Network (EHDN) – Huntington's Disease (the Registry study) in Portuguese sites. The Registry is a multi-centre study, a multi-national OS without any type of therapeutic experiments. The main objective of this network was to collect a huge quantity of data as much as possible and better understand the rare disease to later discover and develop a treatment that slows the progression of Huntington's Disease (68). The Registry is sponsored by the High Q Foundation, a non-profit organisation that supports several research projects with the purpose of find treatments for Huntington's Disease.

The CHLN, E.P.E. – HSM is the Portuguese language coordinator site, this means that it is responsible for coordination and monitoring the study in the Portuguese sites that currently participate in the study. The duties of this activity were divided between two people, the Dra Leonor Guedes and Dra Maria Finisterra. In this context I could follow Dra Maria Finisterra in some of the language coordinator activities.

One of the Dra. Maria Finisterra's roles was to monitor the Registry study in the other Portuguese hospitals. Therefore, I had the opportunity to help her in monitoring activities, such as, verifying data and training the research groups at Hospital Professor Doutor Fernando

Fonseca, EPE and Centro Hospitalar de Lisboa Central, EPE - Hospital de Santo António dos Capuchos.

The other activity of the monitoring was to check online the eCRF and verify some information, only after that did we go to the site and reviewed the data. Some data were collected exclusively in paper and because of that we had to confirm the source documents personally. I had the opportunity to verify the ISF, every patient's ICF and resolve queries with the investigators.

After the onsite monitoring visit we had to elaborate a Monitoring Report Site where we did a follow-up of the visit. After that we sent the report to the EHDN international coordinator group to be reviewed. Simultaneously we sent a descriptive document about what we had done and about the actions that the visited site must do to resolve the discrepancies.

The main goal on the monitoring visit was to verify if the protocol was being followed; if the rights, safety and well-being of patients were being ensured; and if the data was being collected correctly. This activity showed me that the sites have different and efficient ways of being organised.

4.2.4 European Coordinator Meeting

Related to EHDN– Huntington's Disease – Registry I had the opportunity to participate in a European meeting with all main SCs of the participating European countries. This meeting aims that SCs share experience and discuss some doubts and ambiguous questions about the conduction of the study as well as to maintain all countries informed about the position and contribution of the network to the research and development of new treatments for Huntington's Disease.

4.2.5 Pharmacovigilance Activities

The pharmacovigilance is a monitoring area responsible for assessing a medication or therapeutic after their introduction into the marketplace. Thus, when the drug is approved by competent authorities, it is able to be commercialised. However, a continuous verification of the effects in the general population is necessary.

This is an essential process because despite the multiple tests that the medicines are submitted to it is not sufficient to verify all the characteristics and possible reactions of people to the drug. Furthermore, the population sample where the drugs were tested was small size and the collection occurred during a limited time. Because of that only the most usual ADRs (a response to a medicinal product which is noxious and unintended) were expressed, and thus, the safety information known is little (11).

According to the European Commission all medicinal products in the EU once placed in the market must be submitted to assessments so that their quality, efficacy and safety can be verified. This monitoring is fundamental to identify any dangerous behaviour, safety profile of a medicine and consequently the necessary measures in case of danger. This process allows a decrease of risks and an increase of the benefits of medicines.

An URF has activities more restricted than SNF; I had opportunity to verify this fact personally with my presence in a URFLVT. The main activities developed by SNF are: collecting and managing safety data of medicines; looking at the data and detecting reactions; evaluating the data and making decisions; elaborating a risk management plan; protecting public health; communicating with researchers stakeholders and community and making some audits (11).

The main activities of URFLVT involve collecting and treating the data from ADR. Consequently, the URLVT has an implemented system to receive ADR, treat the data and thereafter send them to the Pharmacovigilance Unit in INFARMED.

When I arrived at the unit I was introduced to the group: the header of URFLVT (the clinical coordinator), pharmaceutics and the administrative assistant.

Then I had to read the Management Quality Plan of the URFLVT to understand the structure of the unit, its mission and requirements, vision and activities. This plan allows the proper organisation of the members of the unit, their duties and how to act in specific cases. With a well-structured and effective documentation of all activities the probability of errors and doubt decreases, and consequently the efficiency of the group increases. Since then I have realised the importance of a well-defined structure, function, responsibilities and actions.

After I had known the routine activities I could follow some members in their activities and help them with some procedures. I only participated in pharmacovigilance activities during one month and therefore I only had the opportunity to participate in some activities, such as the routine activities about the reception and treatment of ADRs.

The report of ADR can arrive at the unit by email, phone, fax and letter. Additionally, so that the report can be considered valid, it should include specific minimum data, such as a health

professional identified, a patient, an active substance and a signal of an adverse reaction to a drug. Only if these criteria were met did the pharmacist start the evaluation of the case. After that the report was dated, signed and it was assigned a number code. In case of lack of information the pharmacist contacted the reporter to complete it. In case the report is not received with a standard format the pharmacist must be complete one with the data provided.

After that the report is included in the SVIG and attached to a copy of the original report. In order to thank the reporter, a reply is sent with the confirmation of data reception and acceptance of data. After the reception of the report the causality assessment must be collected and included in SVIG. This causality attribution is performed by the clinical coordinator by considering some factors.

In the instance all data are recorded and added to the SVIG, a summary report is written and the case is officially finalised. An informative email is sent to the pharmacovigilance department in INFARMED to notify a data entry. At the end, the decision is shared with reporter.

During the month I was in URFLVT, I could essentially help the pharmacists in their activities.

4.2.6 Scientific papers writing

It was proposed to me and my colleagues to write together three scientific papers about pertinent concept of clinical research, specifically: “What can we say about Clinical Research Networks?”, “Clinical Trial Monitoring – where do we stand?” and “The Clinical Research Coordinator Activity”.

I had an active participation in the development of the Clinical Network paper and a more secondary intervention in the others.

The purpose of this activity was to investigate some current issue in the research world and understand their reason and influence. We thought these issues were very interesting and updated and due to that we tried to verify all sources available and the authorities’ opinions.

The papers are an effort of a systematic review of the articles published in the scientific literature. We did the search using a publication search tool (OVID) and a specific “key word” according to the research topic.

The paper about Clinical Research Network aims to discuss the strategy, benefits, advantages and the characteristics in order to establish a strong and successful network. The establishment of networks becomes a good strategy to integrate clinical research capacities.

There are some difficulties and obstacles, such as linguistic hurdles and lack of training in clinical research; however, the establishment of partnerships and networks still seems to be a good alternative to optimise resources (economic, human and material) and counter the paradigm that clinical research world is facing (52, 53). Hence, this movement could be a way to minimise the research crisis that the pharmaceutical industry has been facing and despite the evident difficulties in implementing this strategy, it seems the best bet of the research groups (15).

It should also be considered that the networks accelerate a return of benefits to society through the increased knowledge, techniques and biomedical products.

I conclude that due to the crisis in R&D process, it is necessary to innovate, and the development of networks between sites can be a way of improving the current model.

For the development of this paper I had to learn how to create a correct "key word" to search all publications about the theme. After creating a key word I collected a list of references about clinical research networks until March and then I did a pre-selection of the relevant publications according to data presented in the abstract. After that I did a more detailed reading of the papers previously selected and I chose those that seemed to me to approach the issue I wanted to discuss in my work. Then I carefully studied all papers selected and summarised the most important aspects. There are some topics about the paper that I added to the State of the Art of this report, subsection 3.3 Clinical Research Networks.

In order to explain a little what was done and what we concluded in the other papers in which I had a secondary intervention I introduced a small excerpt of them. The one about CT monitoring has the objective of verifying, assessing and criticising the opinion of the research population and competent authorities about the importance of on-site monitoring. The conclusion was that "Clinical trial monitoring" seems to be standing at a crossroads. The sponsors and regulatory agencies are pressing for a more focused and risk adapted monitoring approach to CTs. The fact is that there still exist considerable bottlenecks before these strategies can be used to their full potential. It was verified that not all the CRUs are ready to implement this approach. The implementation of this strategy required the use of more complex electronic data capture to produce, select and analyse accurate data, a more distant contact than the used currently, and more demanding staff training. In addition to these aspects there is the possibility of some CTs could benefiting more from these approaches than others (69).

It is a fact that the on-site monitoring is an expensive activity, generally on-site monitoring performed in industry trials add about 15-35% to the overall costs of a typical phase III trial (70).

Due to the increase of expenditures during the R&D process the CT sponsors have been implementing cost containment measures. It comes as no surprise that alternatives to the costly on-site monitoring are becoming more and more attractive to stakeholders.

The third paper was about the duties and activities of a clinical SC "The Clinical Coordinator Activity", as it has been verified the implementation of a well-organised CRU is extremely important to the success of CTs. When there is a group structured and constituted by qualified people, the rigour and the quality of the data produced are better. It is in this context that a clinical SC role appears. The clinical SC is responsible for conducting research studies and making a bridge between the principal stakeholders.

Through the information collected for this paper it was concluded that the SC position is very gratifying. Most of the SCs enjoy their job and feel that they are very useful to the development of the CTs which they coordinate. (71) This activity is characterised essentially due to the multidisciplinary duties. It is required that the SCs communicate with a wide variety of people, from CT participants to health professionals, administrative technicians, other coordinators and professionals of pharmaceutical industry. The SC has to combine hard skills, which means the knowledge about their area of intervention, and soft skills such as a good capability to communicate, manage, educate, plan and work in team. Additionally, the SCs have to face some ethical questions essentially related to the relationship with patients and they should be able to manage these situations. The SCs' role is very important and some literature refers that "Ultimately, professional research coordinators lead to quality research and more efficient research management" and "coordinators are often described as the most important members of clinical research teams" (72, 73).

Initially the paper was just a narrative; however, after analysing in more depth the importance of the theme we thought that we should transform it into a systematic review but despite the exhaustive work we could not publish that paper. As soon as possible we will submit the papers for publication in a peer-reviewed journal.

In the "Clinical Trial Monitoring – where do we stand? A systematic review" and "The Clinical Research Coordinator Activity" I had a lower participation than in the "What can we say about Clinical Research Networks?" I helped my colleagues in the selection of the key word, gave my opinion about the information to introduce in the paper and verified if anything could be changed and/or added.

4.2.7 Other Activities

Journal Club: In order to complement the scientific knowledge of the research group every Wednesday at 8 am the group met to discuss and share papers, clinical experiences and current themes about Neurology. Every week, one member of the group brought a recent paper about Neurology and Neurosciences and explained to the rest of the group. After that all members shared their opinion, doubts and expectations about the theme.

This meeting also had the purpose to discuss and share some information and problems about the functioning of the team.

Meetings on Wednesday afternoon: Every Wednesday at 6 pm the group had a meeting at LFCT-FMUL with all members of CIC and the Clinical Pharmacology Unit with the purpose of sharing the ongoing and the next projects. Each session, a different member presented one project that they were working on. These meetings allowed keep everyone actualize about on-going projects, discuss, provide feedback and opinions or just share results of the projects.

The first meeting was on 13th November, where everyone introduced themselves and talked a little about the projects where they participated.

5. Discussion

The CTs are an essential practice to obtain the required data to ensure the well-being, safety and quality of patients' life. Through this practice it is possible to know the real efficacy, safety and performance of new drugs in the human body (16). During this training I had the opportunity to understand more about clinical research practice through the conduction of CTs and OSs.

CIC, the host institution, is characterised as a very well-organised unit with 15 years of existence dedicated to clinical research. The CIC is made up of efficient and qualified professionals and consequently all procedures of clinical research are performed in compliance with ethical requirements and regulatory guidelines. The team was very complete, balanced and diversified and despite the fact that the group was made up of several people, they could work in the same direction. This characteristic impressed me because sometimes when the group is big it is difficult to keep everyone focused. The main goal of the research group was to ensure GCP's, safety and well-being of patients, considering the protocol requirements and regulatory issue. Obviously, this strategy had the intention to produce quality data and become the unit into a unit of reference.

The host institution gave me the opportunity to experience the world of investigation, specifically clinical research. This was clearly a very enriching experience in the area. I had the opportunity to work in different departments dedicated to research, do several activities, learn with senior professionals and be in touch with the patients. During the 10 months of training I was mainly involved in several coordination activities required by the protocol in a very large number of CTs and OSs; also I could performed monitoring of an OS; supporting and following daily activities of a pharmacovigilance region unit; supporting a physician in his academic investigation; and developing and preparing a paper about a current theme in the clinical research area.

As a SC I need to mention that I experienced a series of activities linked to the clinical research that allowed me to grow professionally and become a stronger person. There are some things that we can only understand when we are on the field and face real situations.

According my experience I can indicate that the SCs play a very useful role in the research unit. They are responsible for ensuring that the protocol details are followed; entering data; managing patients' anxieties and expectations; assisting the monitors; and connecting

investigators, patients and monitors. The SC contacts with all research team members and also helps during the study submission and coordination.

In the beginning of my activity as SC I had some difficulty in understanding the order and timing of tasks for all studies; identify the research group of all studies; apply some procedures; understand the medical language of the investigators; and understand what activities I could do. However, to overcome these difficulties and doubts I always asked for help when I was not sure of something. Then, when I understood the activities and reached the capacity of playing an active role in CIC I tried to improve the activities learned.

CIC has many different CTs and OSs, as aforementioned. Most of them are in phase II and phase III. This fact supports the Portuguese tendency proved through Portuguese Academic Clinical Research Infrastructures Network studies and PriceWaterHouseCoopers studies (Figure 16) (27, 40, 74, 75). Consequently, my experience in CIC was in phase II and phase III. During my training CIC had conducted a total of 14 CTs of phase III followed by phase II/III with a total of 3 CTs and phase III with 3 CTs. CIC also conducted CTs in other phases; however, in smaller numbers. During my search I verified that CTs of phase I and phase IV were the rarest phases conducted in this unit.

During my training I had the opportunity to contact with new things constantly and I learned throughout the whole period. I considered that every day of the training was a challenge. Due to high number of on-going CTs and OSs, I could contact with a wide range of different procedures to follow. In addition, the several types of visits in each study obliged me to manage several facilities, procedures, information and work closely with the different members of team. I contacted with neurologists, psychologists, SCs, study monitors, statistics technicians, laboratory technicians, nurses, pharmaceuticals and other professionals that the unit had available to ensure the CTs conduction, who were always available to share their experience and help me with their solid background in clinical research. This context also provided me with the advantage of increasing my network of working contacts.

The diversified composition of the research group and the direct contact with the stakeholders of a CRU allowed me to learn a lot and improve my communication competences, organisation skills and knowledge acquired previously, in the Bachelor's Degree and in the first year of my Master's course. Thus, it was possible to apply and complement concepts learned at the university, learn more due a new perspective (on the job) and get prepared for the real world of clinical research.

An efficient communication inside the research group is essential as well as the ability to adapt the speech to patients according to scientific requirements (that usually due to the health limitations of patients is a real challenge). Initially I had a little difficulty but throughout the time I learned how to deal with them. I needed to take care of them with calmness and time, explaining everything the times they asked for or up to the moment I felt they could understand my word (it is essential to adapt the speech to their ability to understand). Thus, I had to learn what I could transmit the information and how I could do it. Another point that I needed to improve was how to manage my feelings. Sometimes it was difficult to maintain the distance between me, as a health professional, and the patient. Some patients were easier than others but in general I think that as a health professional I did a good work with both of them.

I also had the opportunity to improve my communication ability through medical writing activity. With this activity I could complement my experience and expand my knowledge in another area. I learned to search in Ovid and to create a "key word" to search by specific themes, to write a paper and improve my spirit of criticism. I had to confess that it was challenging to do something like that due my difficulty in being objective. However, with this experience I could overcome my difficulties and improve my competences. This was a very promising learning because it seems to me that it will be very useful in the future.

Due to the large number of people I had to work with and the several activities that were my responsibility, I had to develop a scheme of working to ensure that nothing would be forgotten. To ensure an effective and proper function in CIC I developed a table with all the activities I was responsible for, with their respective timings and urgency. This way I made sure that all that I needed was available, well-organised and prepared. The documents required were on the right place, properly signed and dated and the pending activities were not forgotten. Activities such as scheduling appointments, preparing visits, answering calls, clarifying the patients' doubts, verifying the protocol requirements, ensuring patient well-being, respecting sponsor requirements and assisting the monitoring visits were my daily activities and because of that I had to develop my multitasking ability too. Usually in the same working day in CIC it was made several activities. Specifically during the morning it was performed the patients' visits (including the administration of assessment scales, collection of biological samples, and clinical assessment), and the evening was reserved to administrative and logistic activities (including the introduction of data into the CRF, preparation and organisation of future visits, telephone contacts, resolution of queries, and contact with clinical monitor and/or CRO).

All these activities had high importance and due to that I could not fail, any wrong action could compromise the patients' well-being or the accuracy of CT data. As a result I needed to think and react quickly, and improve my critical spirit. Consequently, I gained more sense of responsibility and improved the capacity of judging.

To improve the performance of the unit the studies were distributed among SCs by diseases. However, the SCs, including the SC trainees, must know the protocols of all studies very well. This measure intended to ensure a SC backup for every study, being thus a preventive measure. In case of an unexpected situation in CIC any SC can help or conduct any type of procedure of any study.

I need to refer that my Bachelor's Degree and the first year of Master's Degree were fundamental. They gave me the principal knowledge to work consistently in a professional environment. Much drug legislation, regulatory guidance, laws, ethics documents, physiological, anatomy and physiology concepts that I needed to use were presented to me throughout my previous education. I had to know these concepts to start any clinical practice. I can affirm that thanks to my previous education I could quickly adapt and make continuous progress throughout the 10 months. I could only be an added value to CIC because my background was very complete and prepared me for this position. However, when I arrived at the unit I had to receive specific instructions about CIC and more practical things not taught at school. For example I have not focus before about processing biological samples, performing ECGs and measuring vital signs. This instruction was really important and useful, and in a short time I could integrate in the group.

Regarding the knowledge about the nervous system, I already knew some concepts due to my Bachelor's Degree. However in order to understand the objectives and endpoints of the research studies, to help the investigators and enlighten patients' doubts I had the need to learn more about neurological disorders. Namely, I had to explore about Alzheimer Disease, Parkinson's Disease and Huntington's Disease.

One of the difficulties faced by me in CIC as a SC was the coordination of all professionals required to complete the procedures of the patients' visits. As aforementioned, for the conduction of a single visit several people are needed, and sometimes bringing everyone together or coming up with a timetable that suits everyone is a true challenge. So as to overcome this situation, the SCs and I, tried to schedule an informal meeting with the investigators together to discuss dates. I understood that teamwork is the main ingredient to reach success.

Regarding my participation as a SC I need to mention my pride in working full-time in a CT about Alzheimer's Disease, using an innovative molecule. I was responsible for helping and

following this CT since the initiation visit. Thus, I assisted the PI and other investigators in recruiting patients and later in supporting their participation in the study. This challenge was very enriching due the patients' condition, the demanding requirements, and the characteristics of the CT, I think the unit needs to be enhanced because its great performance. I felt this activity as a challenge and a proof of confidence that I was glad to accepted. To avoid any error the whole procedures were discussed with all members as well as the proper schedule and order of procedures. The enrolment was a very exciting phase because it was our first contact with the potential participant and it was when we offered some potential good to them (when only few options exist). The second phase, when the patient started taking the drug and did complementary exams required, was also an interesting step. It was more demanding and I felt more responsibility. This step required attention and perspicacity to understand the smallest details that could be able to find some evidences of good or bad drug performance.

According to my experience in CIC, the patient (and in some cases the caregiver) showed a high interest in participating in our studies because there are few pharmacological options and at the same time they could contribute to the advance of science and medicine. As a health professional my main interest was to provide the best available service and care to the patients. It was very rewarding to be able to offer some hope to patients and their family.

As aforementioned my experience was more extensive in Alzheimer's Disease than in other neurological disorders presented in CIC. However, I also participated in clinical research in other diseases, and due to that I developed a huge experience in the conduction of neurological studies. There were CTs and OSs for several neurological disorders, with a varied level of complexity, outcomes, procedures, requirements and sponsors by several companies. Due to these conditions I felt privileged because I could work in very different scenarios. I learned a lot with the protocols, applying the procedures required and analysing the data. These activities provided me with the opportunity to complement my knowledge of pathology and to get updated regarding current and innovative treatments available in the market. I strove to have extensive knowledge of pathologies, procedures and interpretation of data and after all this I became able to efficiently do some activities independently. This was a gradual procedure, in which I initially worked by supervision of the SCs, Dra Ana Noronha and Dra Maria Finisterra, and throughout the time I became autonomous and as a result I could participate almost as an official SC in the Alzheimer's Disease CT. Simultaneously, I increased my self-confidence. Throughout this process I also had to evaluate my performance and make some decisions, consequently I had to improve my critical thinking.

Problem solving was another skill I needed to improve to overcome some unpredictable situations. Due to the characteristics of the research group and limited condition of patients sometimes some unpredictable situations happened and it was necessary to improvise.

Regarding the research in Neurology there is evidence that it is a complex area and frightens the pharmaceutical companies. Nowadays there is still a limited knowledge about the nervous system and consequently a restricted understanding of neuropathologies (74). There are many diseases to treat or control, but due to the limited knowledge it has become difficult to develop cost-effective drugs (76). The reality is that this is an area where the development of new drugs is longer and more difficult than usual (25, 29, 49).

Despite non-programmed, the audit was a very important activity for my learning in the area. The unit was contacted when I was already there; therefore, I followed all the preparation steps. The audit is an activity with the objective of identifying problems, errors and implementing corrective and preventive actions. Due to the fact that I was an active member of the team, this activity was very productive and added value to my work.

Regarding my participation in an academic OS I think my participation was positive because I constantly maintained the database updated with new data collected by the investigator. In addition to this activity I developed the capacity of working with SPSS and improved my ability to manage data. I also considered it a big challenge because I never had to work with this program. To become able to work and help the research group I had to learn by myself some concepts and ask the statistical technician for some help. I considered an opportunity to fill the gap in my education.

My participation as co-monitor of an OS (Registry) is also an activity to mention because sometimes I helped the monitor of the study and it was an opportunity to contact with the monitoring world. As a co-monitor I had to go to centres to verify the source documents, emit queries, train researchers and clarify their doubts. Thus, I can build an idea about the role of monitors and their duties. The study was observational, and it was about Huntington's Disease (a neurodegenerative disease with a prevalence in the world of 8-10 per 100,000 inhabitants (77)). It was sponsored by a European network - Euro-HD (the largest Huntington's Disease network). The fact that the focus of the study was a rare disease awakened my interest because I think it is a very noble cause. Working for a Huntington's Disease network was very rewarding as well. It was an honour to help with the collection of data and to contribute to the hope of these patients.

After working for a clinical research network and writing a paper about clinical networks I became a defender of its creation. I think the concept of networks is very promising and can bring

many advantages for the research in Portugal, as previously mentioned in 3.5 Clinical Research Networks. It is therefore urgent to provide some favourable conditions for the establishment of networks.

Doing an overview, my training in CIC was very productive and enabled me to reach all the objectives proposed by me at the beginning of the training. My previous knowledge allowed me to efficiently work and solve some problems that arose. I became a more autonomous, active and self-confident professional with spirit of criticism. Due to the fact that the patients' well-being and safety of has a central role I became more exigent and developed a high sense of responsibility.

During the 10 months of training I could apply my theoretical background and help to produce some data. Throughout the training I based on my knowledge about physiology to understand the neurological disorders, and in the concepts about pharmaceutical R&D process, pharmaceutical legislations and laws passed on throughout the Master's Degree. Due the character of the research group and CIC I developed my communication and organisation skills as well as the ability to do many things in the same working day, being under pressure.

Through my activity as a SC I became more aware regarding the frequent problems in a CRU. For example, after studying the theme I realised that there were some difficulties in recruiting patients. It is a fact that one of the problems in a CRU is the low recruitment of patients. Regarding the Neurology area and in the CIC context, I verified that this situation is not a result of a lack of interest by the research team but it is due to the tight inclusion/exclusion criteria and rigorous design of study.

As a consequence of the characteristics of the host institution I had the opportunity to improve my knowledge in several areas and discover other potential areas of interest.

6. Conclusion

During the training I was able to develop a wide range of activities. Through these activities I could actively work with different groups of work, on different projects, and with people with a diversified background and roles. This fact allowed me to improve my knowledge, learn with experienced professionals and consequently expand my working contacts network.

A CRU is characterised by the agitation of the CT visits, coordination of the procedures according to protocol requirements, and the communication between every member involved in the study visits.

Since I was introduced to participate in many projects and studies in different phases, with different indications and requirements I faced new challenges every day. It is impossible to plan all activities of a day, since some unexpected situation can happen.

Team working is an essential part in the clinical research process. And only thanks to this way of working could I reach my objectives (primary and secondary) and finish successfully my training.

Working in CIC provided me a fundamental and complete background. As a SC trainee I could acquire several skills of coordination because I could actively participate in the daily activities. In this way, every day, I felt the sense of responsibility. I could closely contact with patients, and understand their problems, fears and difficulties. I contacted most of the time with patients with limiting medical condition, such as Alzheimer's Disease, Huntington's Disease and Parkinson's Disease. It was a challenge working with them. Thus, despite the professional learning I also grew up personally. At the same time I acquired technical knowledge about the pathologies and technical procedures.

After this experience I have realised that the CRU is completely responsible for organising the research group. And the SC plays an essential role to ensure a good conduction of studies.

I enjoyed the training due to the good structure of the host institution, the team working spirit, the type of activities developed and the contact with patients. However, sometimes it was difficult because I felt the agony and despair of patients as a first person.

The training as a SC made me gain knowledge and showed me the patients' reality, the daily difficulties of a CRU and the position of Portugal regarding clinical research. It is essential to know the obstacles and realise the reality of our working area; this position provided me both.

Furthermore, I feel much more confidence in accepting new challenges in clinical research in a professional future, and in addition to the hard skills I developed soft skills that will allow me to perform better in the professional context.

Despite the fact that coordination occupied most of my time of training I already need to emphasise the monitoring. I did co-monitoring during short periods but I realised the importance of this position and inherent difficulties. I think that in addition to being a SC, being monitor is also an interesting activity.

The participation in activities of pharmacovigilance in the URFLVT was an excellent opportunity to understand the daily routines of the unit and to know their relevance.

The medical writing activity was another challenge proposed, and I could explore other areas and complement my capacity to search scientific data, organize them and present them in the form of a scientific document.

I would like to add that this experience was very rewarding to me because I felt that directly or indirectly I was contributing to a positive impact in the life of other people.

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