Universidade de Aveiro Secção Autónoma das Ciências da Saúde
Ano 2012

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RELATÓRIO DE ESTÁGIO EM COORDENAÇÃO DE ENSAIOS CLÍNICOS NUM HOSPITAL

REPORT OF TRAINING IN CLINICAL TRIALS COORDINATION IN A HOSPITAL

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Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Dr. Vitor Tedim Cruz, Médico Neurologista no Centro Hospitalar de Entre o Douro e Vouga, E.P.E. e do Professor Doutor José Luís Almeida, Professor Associado Convidado da Universidade de Aveiro.

É com toda a gratidão que dedico este trabalho:

- Especialmente aos meus pais, ao meu irmão e ao Willy por toda a força, apoio, esforço e preocupação;
- A toda a minha família, destacando os meus avós, a Carla, a Joana e as minhas meninas Rita e Beatriz por estarem sempre do meu lado.

A todos vocês, o meu eterno obrigado.

o júri

Presidente

Prof. Doutora Maria Joana da Costa Gomes da Silva
Professor adjunta da Universidade de Aveiro

Prof. Doutor José Carlos Fontes das Neves Lopes
Professor auxiliar da Universidade de Aveiro

Doutor Vitor Pedro Tedim Ramos Cruz
Médico neurologista no Serviço de Neurologia do Centro Hospitalar de Entre o Douro e Vouga – Hospital São Sebastião

Prof. Doutor José Luís de Almeida
Professor associado convidado da Universidade de Aveiro

agradecimentos

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Gostaria de agradecer também ao Dr. Vitor Tedim Cruz pela oportunidade de realizar o meu estágio sob sua orientação, pelo acompanhamento, pelas aprendizagens e pela revisão crítica e conselhos durante a execução deste relatório.

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palavras-chave

Coordenadora de estudos, ensaios clínicos, estudos observacionais, projectos de investigação, artigos científicos.

Resumo

Este relatório descreve as minhas actividades como coordenadora de estudos estagiária, durante 9 meses, no serviço de neurologia do Centro Hospitalar de Entre o Douro e Vouga, em Santa Maria da Feira. Este estágio foi parte integrante das actividades curriculares do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Este estágio permitiu-me desenvolver capacidades de coordenação de ensaios clínicos e estudos observacionais, bem como outras actividades de investigação desenvolvidas, incluindo preenchimento de bases de dados de estudos nacionais e internacionais, participação em projectos de longa duração e artigos científicos.

Para além destas actividades, tive também a oportunidade de participar na validação de um questionário de qualidade de vida para a população portuguesa que sofre de Hipertensão Pulmonar, no Hospital de Santo António, no Porto.

Os conhecimentos adquiridos ao longo de todo o meu percurso académico (licenciatura em Ciências Biomédicas e Mestrado em Biomedicina Farmacêutica) foram extremamente úteis para o desenvolvimento das actividades que me foram propostas e a integração no mercado do trabalho.

Keywords

Study coordinator, clinical trials, observational studies, research projects, scientific articles.

Abstract

This report describes my activities as study coordinator intern, during nine months, in the neurology service of Centro Hospitalar de Entre o Douro e Vouga, in Santa Maria da Feira. This training occurred during the second year of the Pharmaceutical Biomedicine Master at the University of Aveiro.

This training allowed me develop abilities in coordination of clinical trials and observational studies, as well as perform other research activities developed in the neurology service, including filling in of national and international databases of studies, participation in long duration projects and scientific articles.

Beyond that, I also had the opportunity to participate in the validation of a quality of life questionnaire for Portuguese population with pulmonary arterial hypertension, in the Hospital Santo António, Porto.

My background knowledge was useful to develop the activities proposed in the training and to my integration in the working market.

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Abbreviations

AB	Administration Board
ADR	Adverse Drug Reaction
AE	Adverse Event
CAMPHOR	The Cambridge Pulmonary Hypertension Outcome Review
CEIC	"Comissão de Ética para a Investigação Clínica" (Ethics Committee for Clinical Research)
CHEDV	"Centro Hospitalar de Entre o Douro e Vouga, E.P.E." (Hospital Center Entre o Douro e Vouga)
CNPD	"Comissão Nacional de Protecção de Dados" (National Data Protection Committee)
CPI	Critical Path Initiative
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Application
CV	*Curriculum Vitae*
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ERS	"Entidade Reguladora da Saúde" (Health Regulator Entity)
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HSS	*Hospital São Sebastião*
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IMI	Innovative Medicines Initiative
INFARMED	"Autoridade Nacional do Medicamento e Produtos de Saúde I.P." (National Authority of Medicines and Health Products)
IP	Investigational Product
ISF	Investigator Site File
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOC	Level of Consciousness
MA	Marketing Authorization
mRS	modified Rankin Scale
NCE	New Chemical Entity
NIHSS	National Institutes of Health Stroke Scale
NHS	National Health Service
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
POC	Proof-of-concept
RA	Regulatory Authorities
R&D	Research and Development
SACS	"Secção Autónoma das Ciências da Saúde" (Autonomous Section of the Health Sciences)
SAE	Serious Adverse Event
SC	Study Coordinator
SINAS	"Sistema Nacional de Avaliação em Saúde" (National System of Health Evaluation)
UA	"Universidade de Aveiro" (University of Aveiro)
USA	United States of America

WMA	World Medical Association
WHO	World Health Organization

1. Introduction

My internship within the scope of the Pharmaceutical Biomedicine Master´s degree, at the University of Aveiro (UA), took place at the *Centro Hospitalar de Entre o Douro e Vouga, E.P.E.* (CHEDV), from September 2011 to June 2012.

As described in chapter 2, CHEDV includes three hospitals – *Hospital São Sebastião* (HSS), *Hospital Distrital de São João da Madeira* and *Hospital São Miguel* – and it is responsible not only to provide qualified and efficient treatments to patients, but also promotes education, training and clinical research. Neurology service is one of the services that most promotes the performance of clinical trials and contributes to scientific knowledge. So, my internship took place at neurology service of CHEDV.

According to my expectations about the work that will describe later, I established several objectives to be achieved over these months as study coordinator (SC), such as:

- Know and understand procedures behind the functioning of a clinical research site;
- Acquire skills, experience and *know-how* in clinical trials coordination;
- Consolidate the knowledge acquired throughout the academy;
- Integrate scientific background with practice of study coordination and clinical research;
- Contribute to improve clinical research in the neurology service of CHEDV;
- To gather basic knowledge in clinical trials monitoring;
- Establish networking with peers, investigators, monitors, others professionals and institutions;
- Personal and professional developement.

The main training activities were defined earlier in conjunction with my internship advisor, Dr. Vitor Cruz, taking into account the activities and studies already in operation and/ or scheduled to start in the neurology service. The activities defined were:

- Coordination of clinical trials and observational studies (already in operation and scheduled to start) in the neurology service;
- Coordination of international registrations under way in the service;
- Coordination of multicenter research studies in which neurology service participates;

- Collaboration in research activities;
- Collaboration with records of the quality assessment system in stroke.

Additionally, it was also set that my training would be adapted to new activities that will emerge in the service. Prospect new clinical trials for neurology service in the field of movement disorders, such as Parkinson's disease and dementias (including Alzheimer and vascular diseases), was set as a long-term activity.

This report is divided into eight chapters, containing several subchapters. The chapter 1 – Introduction – presents my internship objectives and training plan, as well as the summary of that report. The chapter 2 – Overview of the host institution and clinical trials – describes CHEDV, the neurology service of the hospital and its clinical trials, while chapter 3 – State of the art of the clinical research – includes the state of the art of the Research and Development (R&D), clinical trials history and its classification. It also contains an overview about clinical research in Portugal and around the world. The chapter 4 – Clinical research – experience as SC – initiates the description of my activities during the internship. The remaining tasks performed during my training in the hospital are reported in the chapter 5 – Other projects and collaborations. The chapter 6 – Validation of the questionnaire: "The Cambridge Pulmonary Hypertension Outcome Review" (CAMPHOR) for Portuguese population – contemplates an extra activity conducted in another hospital. Competences and know-how acquired with the internship are described in the chapter 7 – Discussion. My internship contributes to increase of clinical research in the neurology service of CHEDV, so I would like to keep working as SC in this hospital. That conclusion are presented in chapter 8 – Conclusions.

2. Overview of the host institution and clinical trials

This chapter presents a description of the host institution – CHEDV – its structure, activities and its role and performance in clinical research.

2.1. Overview of the host institution – CHEDV

CHEDV is based in Santa Maria da Feira and includes three hospitals: HSS (Santa Maria da Feira), *Hospital Distrital de São João da Madeira* and *Hospital São Miguel* (Oliveira de Azeméis) (table 1). Its development resulted from the publication of the *Decree-Law 27/2009, of January 27th*, which officially came into force on 1st of February 2009, in order to better articulate the hospitals of the northern district of Aveiro, improve access to specialty external consultations, facilitate the management of surgery waiting lists, streamline human and materials resources, ensure greater safety of the patients and facilitate professional recruitment[1-3]. These measures promote economic and financial sustainability of the National Health Service (NHS)[2]. Thus, CHEDV became responsible for providing healthcare to people living in Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva (part of the villages), covering around 340.000 inhabitants[1].

The development of CHEDV involved rewording the organizational structure of these three hospitals, transferring functions and responsibility of management, services and logistics to just one leadership (figure 1). This reorganization was based on the implementation of three strategic principles: focus on proximity, ensure maximum patient safety and promote efficiency. All logistic support services are centralized in HSS and the remaining two hospitals provide multifunctional services of general support. The activities of these health entities are guided by values, such as: respect for the individual, quality, performance, innovation and ethics[2].

Table 1 – Chronology of the three hospitals that compose CHEDV[1].

CHEDV		
HSS	**Hospital de São João da Madeira**	**Hospital São Miguel**
• **1999** - On January 4th, HSS initiated its functions; • **2002** - HSS was transformed into a corporation of exclusively public capital; • **2005** - HSS became a public enterprise entity; • **2009** - On February 1st, HSS was included in CHEDV.	• **1966 -** The hospital was opened on June 1966, by initiative of local *Santa Casa da Misericórdia*; • **1975 -** The hospital became part of the NHS; • **1977 -** The institution became part of the *Centro Hospitalar de São João da Madeira/Oliveira de Azeméis*; • **1979 -** It integrated *Centro Hospitalar de Aveiro Norte*; • **1989 -** The hospital center mentioned above was dissolved and the hospital gained administrative and financial autonomy again; • **2009 -** This hospital was included in CHEDV.	• **1875 -** This hospital initiated functions on July 1st, through donations of the local *Santa Casa da Misericórdia*; • **1975 -** The hospital became part of the NHS; • **1977 -** The health entity became part of the *Centro Hospitalar de São João da Madeira/Oliveira de Azeméis*; • **1979 -** It integrated *Centro Hospitalar de Aveiro Norte*; • **1989 -** The hospitalar center was dissolved and the hospital gained administrative and financial autonomy again; • **2009 -** This hospital integrated CHEDV.

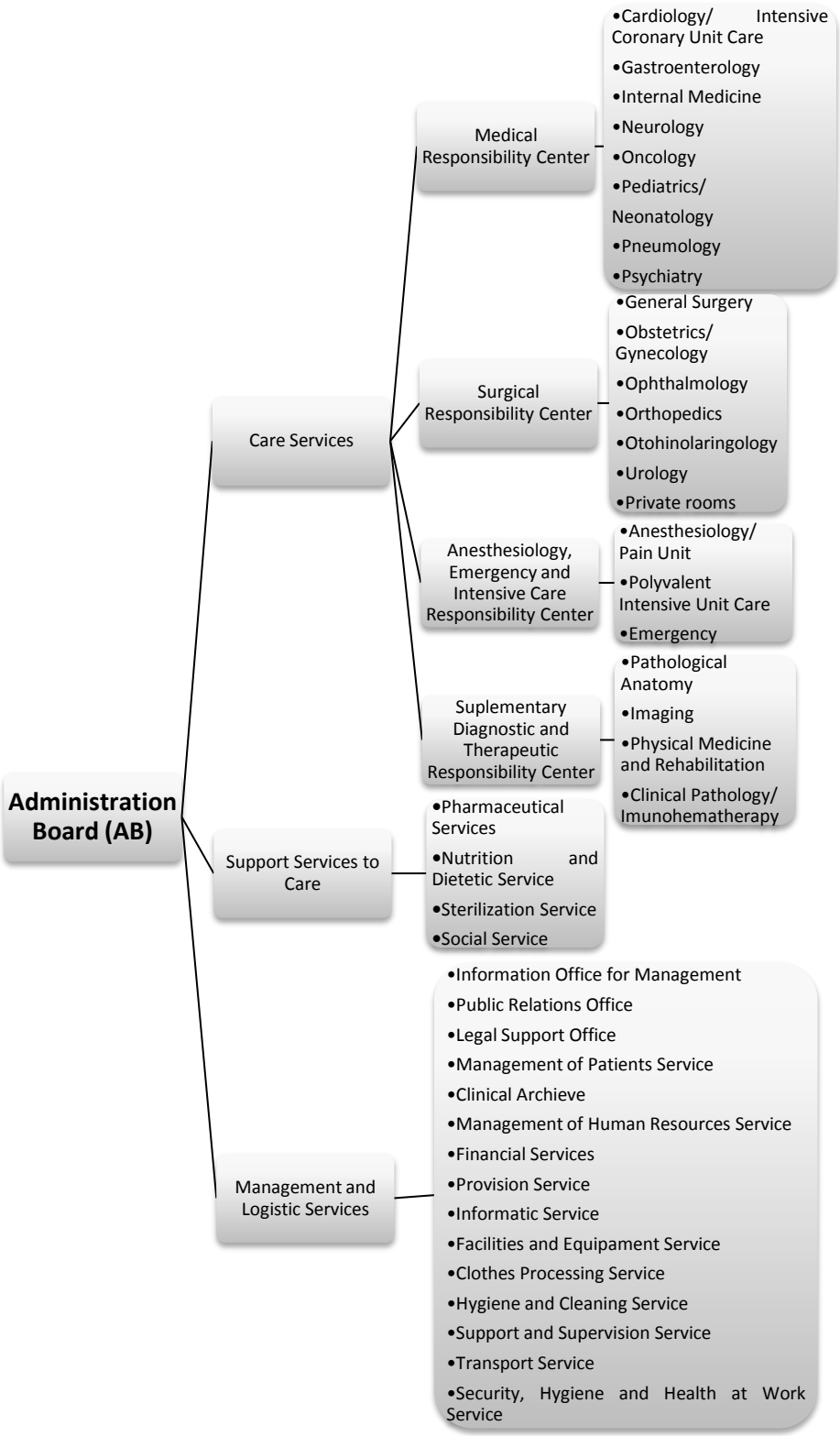

Figure 1 – Description of the organization of CHEDV; AB – Administration Board (adapted to reference 2).

HSS succeeded the *Hospital Nossa Senhora da Saúde de São Paio de Oleiros*, which was gradually ceasing functions by transferring services and professionals to HSS. The new hospital initiated functions on 4th of January 1999, after the publication of the *Decree-Law 151/98, of June 5th*, and it was an innovative way to manage a Portuguese hospital. Therefore, HSS benefits from a management model, whose legal status allowed the implementation of enterprise management in a set of hospitals of the NHS[1, 4]. So, private management rules, methods, techniques and instruments are applied to HSS, always ensuring public interests. Private management aims to increase efficiency, while decreasing healthcare costs[5].

Private management essentially implies two key differences when compared with the remaining entities of NHS:

- Individual employment contracts;
- Greater flexibility in supply relationships (greater streamlining in the processes of acquiring goods and services)[4].

Furthermore, the private management model applied in HSS also allows granting incentives (monthly productivity bonuses and research grants) to healthcare professionals, and contract with Health Ministry according to production goals defined[1].

The adhesion to the incentives system allows private consultations inside the hospital and it also led to increased motivation of staff, development of team spirit, alignment of individual interests with management objectives and increased productivity[4].

The internal organization of HSS is also an area of great freedom of management, contrary to what traditionally happens in other NHS's hospitals. HSS departments were arranged into four major cost centers, which were divided into services. Cost centers were responsible for preparing the annual program of activities for each service, where it generated a proposal to the NHS/ Health Ministry. Organization of emergency service was also significantly different, which included the first procedure of hospital screening to improve healthcare[4]. So, HSS implemented the Screening System with Manchester Priorities, in which patients are treated according to the severity of the clinical situation, instead of considering the arrival order to the hospital. The severity of clinical situation was defined following a protocol that classifies each patient with a color (red – emergent, orange – very urgent, yellow – urgent, green – little bit urgent, blue – not urgent) and there is a waiting time recommended for each color (immediate care, 10 minutes, 60 minutes, 2 hours and 4 hours, respectively)[6].

Taking into account the structure of the hospital, HSS comprises several councils and bodies responsible for managing the hospital. So, HSS includes in its structure: general counsel, administration bodies, technical management bodies, supervisory body and technical support bodies[5].

Despite not being part of CHEDV, *Hospital Francisco Zagalo*, in Ovar, still works in straight collaboration with HSS. Since there is no emergency service, pediatric emergency, pediatric inpatient or other medical specialties, like neurology, at *Hospital Francisco Zagalo*, these became the most striking areas of collaboration between these two hospitals[2].

Until now, CHEDV was presented as an institution responsible for providing qualified and efficient treatments to patients, taking into account economics sustainability of the NHS. However, the Director's Board of CHEDV also considers as essential mission promotion of education, training and clinical research. The hospital promotes the performance of clinical trials, which contribute to increase scientific knowledge and development of better therapeutics and methodologies. R&D are usually funded by private enterprises and, according to the accounts report of CHEDV in 2010, these activities implicated no expenses to the hospital[2].

2.2. Overview of the host institution – neurology service of CHEDV – and the clinical trials

My internship as study coordinator was centralized in the neurology service of CHEDV, in Santa Maria da Feira.

Neurology is a medical specialty responsible by the diagnosis and treatment of disorders of the nervous system (includes brain, spinal cord and nerves)[7]. In order to guarantee efficacy, safety and quality of healthcare, the neurology service has several human resources:

- Senior neurologists (seven):
    - The director – Dr. Leal Loureiro;
    - Two graduated assistants;
    - Four hospital assistants;
- One additional neurologist (responsible by spasticity, dystonia and botulinum toxin clinic);
- Neurology residents (seven);
- One neuropsychologist (including among one to three psychologists in training);

- One neurophysiology technician;
- One ultrasound and vascular Doppler technician.

Human resources, as well as appropriate equipment and facilities, are critical for the efficiency and quality of the activities undertaken by the service. Neurology service covers a wide range of activity areas from diagnosis and patient treatment to education and training, defining as primordial areas the emergency service and stroke fast track, stroke unit and general neurology ward (inpatient), day hospital and external consultations. Each of these areas may be (or not) subdivided into more specific areas (figure 2).

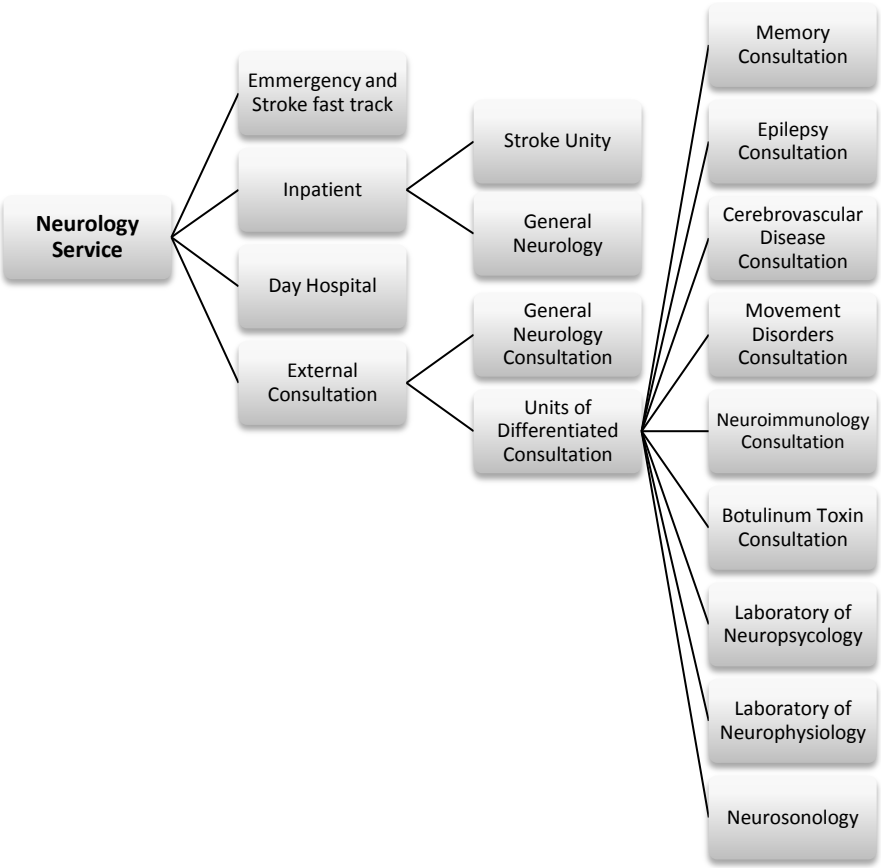

Figure 2 – Primordial areas of activity of the neurology service at CHEDV.

Furthermore, this service also encompasses other work areas, oriented to the organization, education and training:

- Internal advice;
- Making reports of external consultations;
- Meetings and organization of differentiated consultations;

- Maintaining in functioning supplementary means of diagnosis: electroencephalogram and cervical and transcranial eco-Doppler;
- Support nursing visits post-stroke;
- Orientation of the neurology residents;
- Orientation of the general and family medicine internal experts;
- Participation in pre-graduate teaching (along with UA);
- Preparation of clinical topics and presentations at conferences;
- Three doctoral thesis in progress (by three neurologists);
- Two master thesis (by one internal expert and the neuropsychologist);
- Programming and implementation of development projects in the service;
- Support service management;
- Clinical research, including clinical trials.

Clinical research can be defined as the research that involves a particular person, a group of people or human samples/materials[8]. The history of clinical research of the neurology service of CHEDV is not too long, being the oldest records dated from 2004. Thenceforward, this service has been involved in clinical trials, observational studies and long duration projects and until September 2011, there was conducted and/or approved a total of seven clinical trials:

- **Vipe** – Valproate in Partial Epilepsy: phase IV clinical trial conducted from 2004 to 2005;
- **PRA/BIA 2093-303 –** Efficacy and safety of Eslicarbazepine Acetate as Adjunctive Therapy for Refractory Partial Epilepsy: phase IV clinical trial carried out from 2004 to 2006;
- **ECASS-III** – Placebo controlled trial of alteplase (rt-PA) in acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4,5h after the stroke onset: phase IV clinical trial conducted from 2006 to 2008;
- **IST 3** – International Stroke Trial 3: phase IV carried out since 2008;
- **ICTUS** – International Citicoline Trial on Acute Stroke: phase III clinical trial performed from 2007 to 2012;

- **MACSI** – Membrane-Activated Chelator Stroke Intervention: phase III clinical trial conducted from 2010 to 2012;
- **CAROLINA** – CARdiOvascular safety of LINAgliptin versus glimepiride in patients with type II diabetes mellitus at high cardiovascular risk: phase III clinical trial initiated in 2011.

Comparatively with clinical trials, the service has been just involved in two observational studies:

- **SITS-MOST** – Safe Implementation of Thrombolysis in Stroke Monitoring Study: performed in 2005;
- **PORTYSTROKE** – Screening genetic conditions in PORTuguese Young STROKE patients: from 2005 to 2008 (follow-up from 2011 to 2012).

Furthermore, neurology service also has been involved in eight long duration projects, such as:

- **SITS-ISTR** – Safe Implementation of Thrombolysis in International Stroke Thrombolysis Register: from 2005;
- **"Freeze the stroke"** – Validation of an information strategy for the population of the warning signs for stroke, from 2007 to 2009;
- **Novel SPG3A and SPG4 mutations in dominant spastic paraplegia families** (2009);
- **SWORD** – Stroke Wearable Operative Rehabilitation Devices: clinical development and validation of an intelligent vibrating device for outpatient use in rehabilitation of stroke patients;
- **COGWEB** – Conception and validation of a website to support memory consultation;
- **SINAS** – National System of Health Evaluation ("Sistema Nacional de Avaliação em Saúde"): since 2011;
- **Alu elements mediate large SPG11 gene rearrangements**: further spactasin mutations (2012);
- **Autosomal dominant spastic paraplegias**: a review of 89 families resulting from a Portuguese survey (2012).

The clinical research of the neurology service of CHEDV can be also classified in external initiative projects or local investigator initiative projects. All clinical trials and observational trials performed until now are part of external initiative projects together with some of the long duration projects, such as:

- SITS-ISTR;
- SINAS.

Otherwise, local investigator initiative projects comprise the remaining six long duration projects, like:

- “Freeze the stroke”;
- Novel SPG3A and SPG4 mutations in dominant spastic paraplegia families;
- SWORD;
- COGWEB;
- Alu elements mediate large SPG11 gene rearrangements: further spactasin mutations;
- Autosomal dominant spastic paraplegias: a review of 89 families resulting from a Portuguese survey.

Most of the research projects conducted in the neurology service of CHEDV were external to the hospital initiative. From the total of 17 research projects, six were developed by one or more investigators of the neurology service. Despite the difference, investigation members of the service are motivated to develop their own ideas and contribute to science progress.

Notwithstanding still recent experience in clinical trials, it is possible to conclude that the number of phase III and phase IV studies approved is similar; although most phase IV clinical trials have been conducted. Phase I and phase II clinical trials were not carried out in the service.

Relatively to the investigation areas (figure 3), the neurology service has shared the research efforts among six areas, highlighting cerebrovascular diseases.

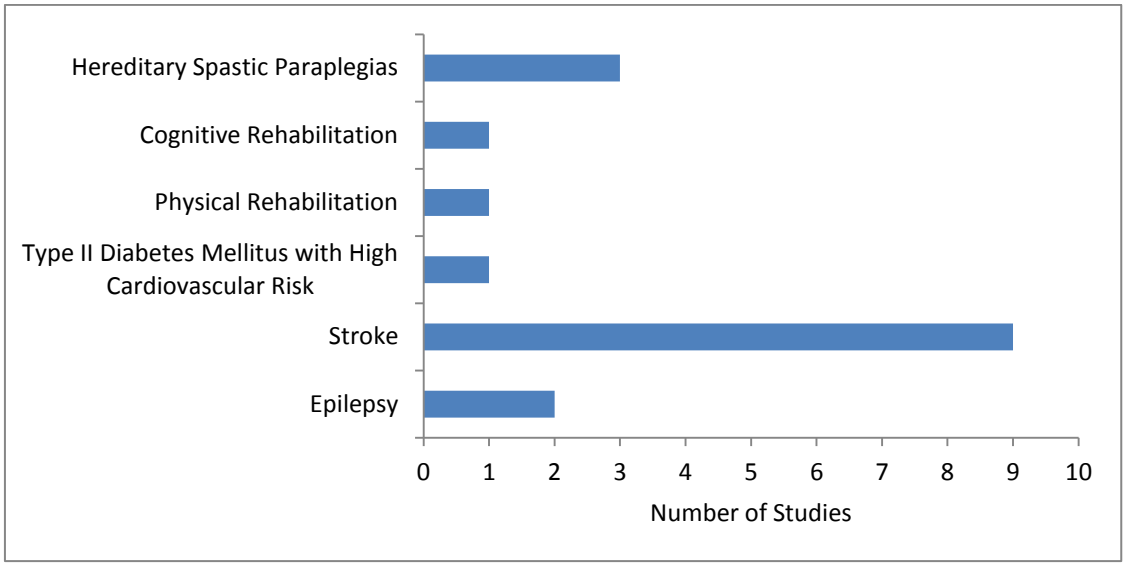

Figure 3 – Distribution of the clinical trials and projects carried approved in the service by research areas.

2.3. Potential of the neurology service to recruit new clinical trials

As stated above, in the neurology service, there were several studies covering a variety of neurological areas, as hereditary spastic paraplegias, cognitive rehabilitation, physical rehabilitation, stroke, epilepsy and type II diabetes mellitus with high cardiovascular risk. However, neurology has more topics that can be investigated. So, it is important to perceive the availability of patients to recruit previous to the initiation of studies. Patients are usually identified and recruited from the outpatient clinic and emergency service.

The neurology service has specific types of external consultations according to the disease. So, I decided to use the number of consultations performed from 1st of January 2012 to 30th June 2012 to analyze the potential of the service to recruit new clinical trials (figure 4).

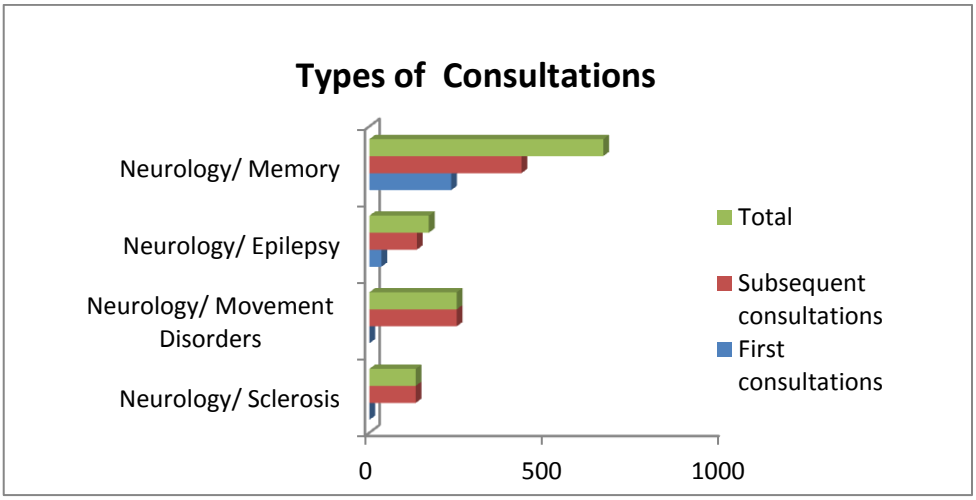

Figure 4 – Description of the consultations performed into the neurology service from 1st January 2012 to 30th June 2012.

According to this data, it is possible to conclude that diseases that affect memory are the most represented in the service. So, this can be an excellent area to research. Despite of the big difference, movement disorders, which include Parkinson disease, can also be a good area to investigate. Epilepsy and sclerosis does not present the same availability of patients to recruit, which can limit the number of clinical trials performed. Notwithstanding, this is not an exclusion reason to all clinical trials.

So, with motivation and efforts of the neurology service staff, the hospital has potential to improve clinical research.

3. State of the art of the clinical research

This chapter describes the state of the Pharmaceutical R&D and the evolution and classification of clinical trials. Beyond that, it presents a review of the clinical research in Portugal and around the world.

3.1. Introduction to the pharmaceutical R&D

New medicines are essential components in healthcare and therapeutic practices since the earliest times, contributing to improve people´s quality of life and extend life expectancy. Currently, innovative drugs have contributed to reduce the death rate for diseases[9]. So, innovation in drug development is central to increase quality, safety and efficacy of the healthcare.

Pharmaceutical R&D is defined as the process of discovering, developing and introducing in the market new drug products[10]. Thus, it is a process organized in phases, since drug discovery until post-launch activities (figure 5)[9, 11]. Earlier identification of the characteristics of the investigational product (IP) and planning its development according to the required profile is essential to an efficient drug development[12].

Figure 5 – Phases of R&D (adapted to reference 9).

In recent decades, traditional drug R&D is confronted with several problems to develop new chemical entities (NCE): high costs, complex regulatory environment, huge development time (approximately 12-13 years), “productivity gap” (investment increasing, while the numbers of new medicines decrease), high failure rates, “output stagnation” (although the increase of developing medicines costs, it is difficult to find really innovative new products) and low ability to predict safety and efficacy. Despite of relatively stability in development time of new drugs during the last

two decades, R&D time increased substantially from 1960s until now. Larger and more complex clinical trials also increase resources investments and consequently enlarge R&D costs[11, 13, 14]. Even though high R&D costs, it has been verified a decrease of approximately 50% in the submission of new medicines, due to lack of efficacy and safety of NCE (especially in phase II and phase III). Moreover, some drugs introduced in the market may show inefficacy in populations with certain characteristics[15, 16]. Thus, R&D needs to be improved and a new development paradigm should emerge.

Two international initiatives, *"Critical Path Initiative"* (CPI) from United States of America (USA) and *"Innovative Medicines Initiative"* (IMI) from Europe, have been developed to improve drug development and promote better medicines[17, 18].

Therefore, Food and Drug Administration (FDA) develops the CPI, which combines efforts of the government, industry, academy and patients to increase efficiency and productivity of the R&D processes, create an innovative science and reduce uncertainty, applying new scientific tools. This initiative is based in 6 topics:

- Topic 1: Better Evaluation Tools – Developing new biomarkers and disease models;
- Topic 2: Streamlining Clinical Trials: involves innovative clinical trial designs to assess improvement of health or the occurrence of adverse drug reactions (ADR) – "learning trials";
- Topic 3: Harnessing Bioinformatics: implies the use of mathematics, statistics, computational data analyses and biological data to develop robust computer models of the human physiology and diseases;
- Topic 4: Moving Manufacturing into the 21st Century: aims to improve efficiency and quality of manufacturing, using tools to identify and analyze critical products attributes;
- Topic 5: Developing Products to Address Urgent Public Health Needs: antibiotics and countermeasures to combat emerging infections and bioterrorism;
- Topic 6: At-risk Populations – Pediatrics: development of therapies for children and adolescents[17].

Similarly, European Medicines Agency (EMA) develops the IMI, which aims to promote faster R&D of better medicines and improve cooperation and competition among pharmaceutical companies.

The initiative was developed through the collaboration between public and private sector, including biopharmaceutical companies, regulators, academy and patients. It consists in 4 pillars:

- Pillar I: Improve Predictivity of Drug Safety Evaluation;
- Pillar II: Improve Predictivity of Efficacy Evaluation;
- Pillar III: Knowledge Management: improve information and data utilization;
- Pillar IV: Education and Training: resolution of training gaps[18].

There are several concepts transverse to this both initiatives and simultaneously applicable to the modern paradigm – *"Quick win, fast fail"* (figure 6).

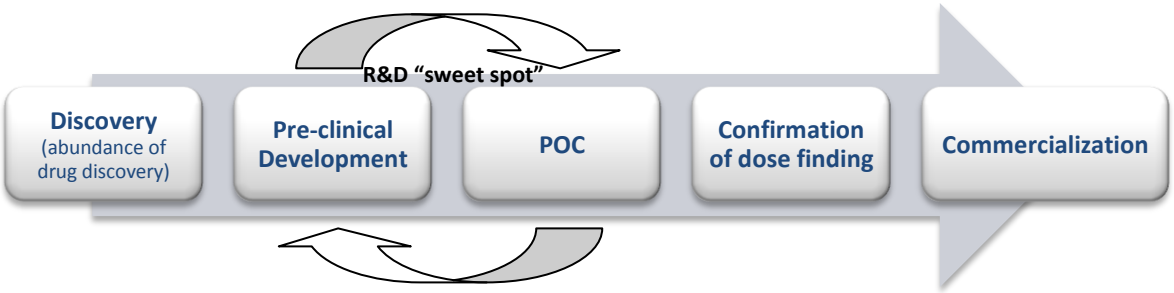

Figure 6 – "The quick win, fast fail drug development paradigm": an alternative development paradigm (adapted to figure 5 from reference 19).

"Quick win, fast fail" drug development paradigm aims to reduce drug uncertainties, before the expensive later development stages (phase II and phase III) through the establishment of proof-of-concept (POC). These are studies performed earlier in drug development, after choose the drug target (preferably in phase I) to evaluate molecule-target binding ability and pharmacological activity in human body. So, it causes a reduction in the number of compounds advancing into phase II and phase III. However, the probability of success and introduction in the market of those that progress in the development increases substantially (advance of the NCE with established efficacy and safety). This paradigm contributes to reduction of attrition rate and costs. Costs savings are useful to enhance R&D productivity[19]. Through better target selection (more validated and druggable targets), this process can be optimized. Both efficacy and safety biomarkers (measurable characteristic that reflect physiological, pharmacological or disease processes) are useful in disease diagnosis, identification of target population, dose selection, duration of treatment and safety concerns. Thus, biomarkers are indispensable to "go/no-go decisions", a process that contributes to quick identification of pharmaceutical candidates with

high probability of fail and those with good chances of success. It allows redirecting development efforts to promising candidates[17, 19]. New *–omic* technologies, such as genomics, metabolomics and proteomics, are relevant as biomarkers source[17].

In addition to this information, collaboration among regulatory authorities (RA), stakeholders and biopharmaceutical companies are essential to the success of R&D.

3.2. Overview of the clinical trials history

According to the history records, James Lind, a ship's surgeon in the British Navy, was who first carried out a controlled clinical trial. In 1753, this was recorded as an open trial using just few patients, without placebo control and almost with no costs. Despite of being very modest and rudimentary, this trial possibly stimulated permanent changes in clinical practice until nowadays: randomized, double-blinding and placebo-controlled clinical trials[20]. Clinical trials have been shaped over the time also by the action of technological and scientific progression, historical disasters and ethical concerns. The harmful experiments performed during the Second World War (1939 – 1945) without informed consent, causing pain and death and with no benefits to the participants led to the development of the Nuremberg Code (1947), a set of guidelines for medical experiments[21]. Nuremberg Code was the basis to the development of the Declaration of Helsinki by the World Medical Association (WMA), in 1964. Declaration of Helsinki is a document of ethical principles for medical research involving human patients. This ethical statement is reviewed every 4 years[21, 22]. In the mid of 50s and 60s, thousands of children born with phocomelia due to the use of a drug – thalidomide – prescribed to treat morning sickness in pregnant women. Thalidomide disaster alerted the public authorities to the need of better monitoring of drugs and more regulations[23, 24]. This tragedy booted the development of pharmacovigilance, defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects (AE) or any other drug-related problem"[24, 25].

Therefore, it is possible to conclude that laws, regulations, guidelines and ethical considerations are essential to ensure safety, quality and efficiency of NCE. One of the guidelines with special interest related to clinical trials is ICH Topic E6 (R1) – Guideline for Good Clinical Practice (GCP). In accordance with this standard, GCP is defined as "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects". Compliance with the established assumptions assures "that rights, safety and

well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible"[26]. This standard was established by the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH), which brings together the RA and pharmaceutical companies of Europe, Japan and USA, to discuss and develop quality, safety, efficacy and multidisciplinary aspects[27].

3.3. Clinical trials classification

According to ICH Topic E6 (R1) – Guideline for Good Clinical Practice, a clinical trial/study can be defined as "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy."[26]. As mentioned by WHO, each health-related intervention evaluates the effects on health outcomes and may include "drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc."[28].

Clinical trials are usually classified into four temporal phases: phase I, phase II, phase III and phase IV. However, it is essential realize that temporal classification does not imply a fixed order of studies. Therefore, a classification system based on study objectives is preferable: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use. These two classification systems are closely correlated[12]. In this way, clinical trials are classified into:

- **Phase I – Human Pharmacology:** corresponds to the initial administration of IP into humans usually with non-therapeutic objectives, to determine initial safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD). As secondary objective, these studies can also measure early potential therapeutic benefit. This phase is carried out in small groups of healthy volunteers and, exceptionally in potentially toxic drugs are recruited patients[12, 20];
- **Phase II – Therapeutic Exploratory:** corresponds to studies conducted in patients with target disease (using relatively narrow criteria that leads to homogeneous population) to explore therapeutic efficacy. In this phase, it is determined and evaluated dose, regimen,

potential endpoints and target population for subsequent clinical trials (phase III). This phase enrolls larger groups of patients (several hundred patients)[12, 20];

- **Phase III – Therapeutic Confirmatory:** the primary objective of this phase is to demonstrate or confirm therapeutic benefit of the drug. So, phase III clinical trials intend to certify the preliminary evidences of the phase II – safety and effectiveness in the target indication and population – and provide basis for marketing approval. The studies are conducted in larger groups of patients (hundreds or thousands of patients)[12, 20];
- **Phase IV – Therapeutic use:** these studies are important to optimize drug use, but there are not needed for drug approval. So, this phase is initiated after the marketing authorization (MA) of the IP. The main objectives of the studies are: surveillance of efficacy and safety and comparisons with other treatments associated considering long-term use of the drug and "real-life" conditions[12, 20].

3.4. Clinical research around the world

Clinical research is the investigation that can be either performed in humans (individual people or groups of population) or materials of human origin, such as observed behavior, tissue samples or specimens, to develop methods to diagnose, treat and make a prognosis of several pathologies. It implies direct contact with volunteers, after assignment of informed consent, and can include the study of: mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies, epidemiological and behavioral studies, outcome research and health service research[29, 30]. Clinical research is generally performed in hospitals or others healthcare units – research sites – including public or private institutions, laboratories or other entities that are endowed with human and materials resources required to conduct clinical trials, on national territory or another Member-State[31]. So, clinical research sites should be adequately structured and equipped with qualified staff, such as healthcare professionals, technicians and SCs, in order to facilitate the conduction of the studies[31].

The development and implementation of well-structured facilities to perform clinical trials is one of the most important efforts to increase the number of clinical trials and contribute to commercialization of efficient and safety new drugs.

In recent years, many other efforts have been made to produce more and better medical products. However, the path taken from development to mass-production and commercialization

has become ever more challenging, inefficient, expensive and lengthy[32]. The increase of qualified innovative products and the development of cost-effective medicines are keys to face R&D challenges[19]. As stated above, the initiatives that have been developed by the FDA and EMA, CPI and IMI respectively, have an essential role to quickly develop more effective and safer human medicines[9, 17].

Furthermore, biopharmaceutical industry is now experiencing the globalization of the clinical trials. Trials are moving from developed countries, such as USA and Western Europe to third world countries. Thus, it has been observed a reduction in the proportion of clinical trials conducted in these areas. Cost savings have been appointed as one reason to clinical research increase in the emerging countries, due to lower salaries of the physicians, nurses and SCs. Additionally, developing countries are expanding markets due to high population size, which conducts to high recruitment rates (availability of large pools of potential trials participants), less bureaucratic and cheaper regulatory environment. So, emerging countries increase the investment returns. In conclusion, it is important to streamline clinical trials regulations, in order to reduce redundancy while ethical considerations are guaranteed[33].

3.5. Clinical trials in Portugal

Similarly to the situation described above, in Portugal, R&D is also facing a crisis period. There is stagnation in development of new medicines and is growing the need to develop more efficient, safety and innovative medicines. So, it is necessary to increase clinical trials performed in our country. However, the low recruitment rates, bureaucracy and regulatory environment constrain the conduction of studies in Portugal and favor its distribution to emerging countries. Therefore, it has been observed a reduction in the number of trials performed in Portugal. The decline of clinical trials has been also noticed by Portuguese media: “Bureaucracy and scarcity of healthcare professionals in hospitals delay approval of processes until six months. Industry chooses quicker countries (…) mainly Eastern European countries, such as Ukraine and Romania” in *Diário de Notícias* on 6th of November 2009[34].

National Authority of Medicines and Health Products – *“Autoridade Nacional do Medicamento e Produtos de Saúde I.P.”* (INFARMED) – is the entity responsible for MA of human medicines, in Portugal, while clinical trials authorization depends on the INFARMED and positive opinion of the Ethics Committee for Clinical Research (CEIC)[35].

The INFARMED has available some statistic data about assessment of the clinical trials. According to the accessible data, antineoplastic and immunomodulating agents represent the area where there have been performed more clinical trials in Portugal. Beyond that, antiinfectives agents and drugs for nervous systems are the next more representative areas in clinical trials. An exception was verified in 2011, since the number of clinical trials related with blood and blood forming drugs has undergone a significant increase[35].

Analyzing data from 2006 to 2011, it is possible to observe a decrease in the number of clinical trial applications (CTA) submitted and authorized by the authority. It is not noted a significant change in the average time for authorization (figure 7)[35].

Analyzing statistic data by clinical development phases, a huge difference between phases is verified. Even though the global reduction in the total number of clinical trials approved, phase III maintains the largest number of clinical trials in Portugal, while percentage of phase IV clinical trials decline (figure 8)[35].

Despite of the decline in the number of the clinical trials performed, there has been a significant increase in the substantial amendments notified for INFARMED (figure 9)[35].

The reduction in the number of the studies demonstrates lost of competitiveness to emerging countries. To be successful in the studies, Portugal needs to select the best clinical research sites, with best recruitment rates (higher and faster recruitment).

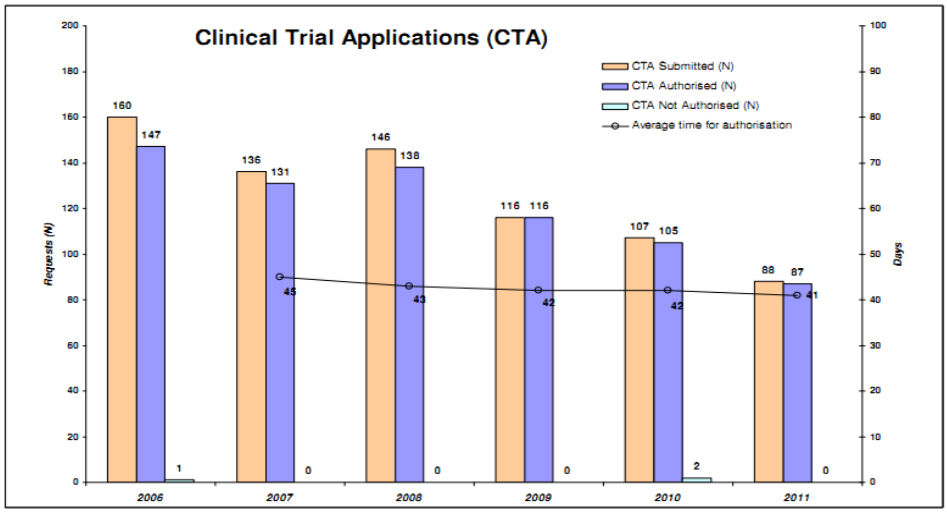

Figure 7 – Number of CTAs submitted and authorized by the INFARMED, between 2006 and 2011 (reproduced from reference 35).

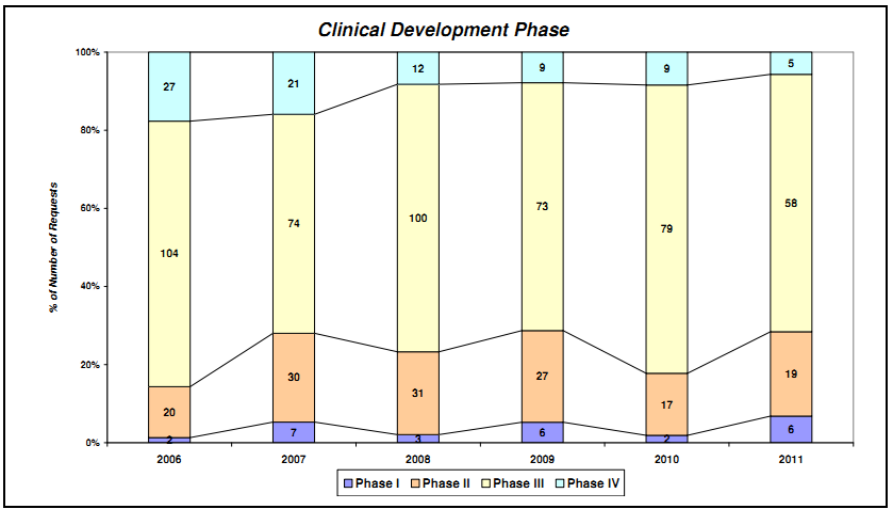

Figure 8 – Total number of clinical trials approved by phases, in Portugal, between 2006 and 2011 (reproduced from reference 35).

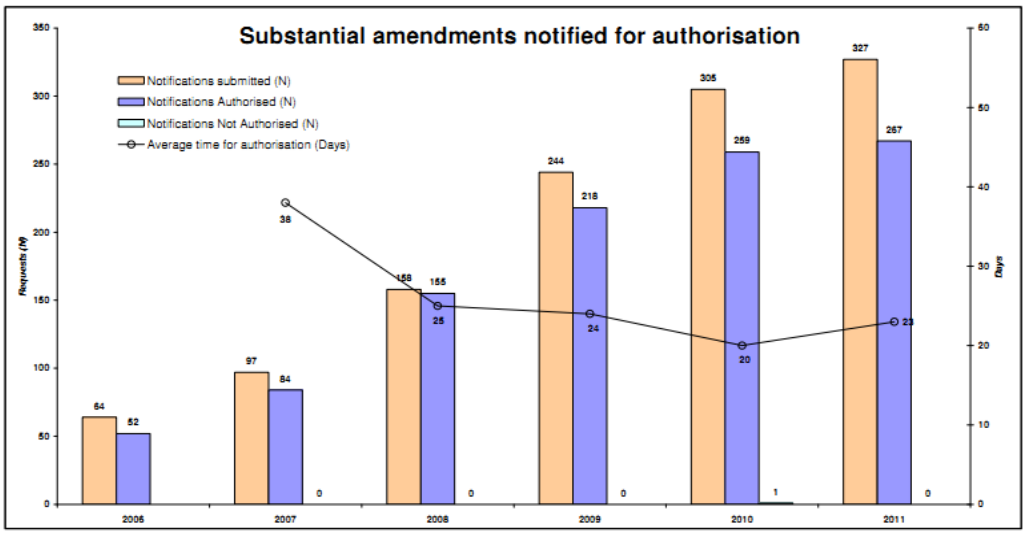

Figure 9 - Number of substantial amendments notified for authorization (reproduced from reference 35).

4. Clinical research – experience as SC

My internship in CHEDV was mainly focused on clinical research of the neurology service. Thus, this chapter addresses clinical research and describes activities performed as SC.

The neurology service is composed by a medical team, committed to provide high level of healthcare and contribute to science and knowledge evolution. Currently, the service is involved in clinical trials, observational studies and research projects, constituting clinical trials the most representative area of investigation.

In this context, I carried out SC activities, from assessment, initiation and conduction of studies to its completion.

At the starting point of my internship, it was introduced the hospital facilities and clinical research teams. Once there were several ongoing studies in the service, I started gradually in each study according to the workload.

4.1. General training

At the beginning of the training, I firstly researched and tried to understand some scales used to evaluate physical and neurological deficits of the patients, since these are often used in the conduction of clinical studies in neurology.

The modified Rankin Scale (mRS) is a post-stroke functional assessment scale, composed by seven levels, from zero to six, being zero the normal stage (0 – no symptoms at all; 1 – no significant disability; 2 – slight disability; 3 – moderate disability; 4 – moderately severe disability; 5 – severe disability; 6 – death). Each one of these degrees allocates distinct abilities and disabilities. This is the most used scale to assess stroke outcomes in clinical trials[36].

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool, developed by national and international government entities and private and academic organizations, to quantify stroke-related neurologic deficits. Although it was initially developed as research tool for acute stroke clinical trials, NHISS is also extensively used as a clinical assessment tool to evaluate short and long neurological deficits (lesion size and stroke severity) in acute stroke patients. NHISS is a simple, valid and reliable tool, composed of 15 items: level of consciousness (LOC), LOC questions and commands, best gaze, visual field, facial palsy, motor arm and leg, limb ataxia,

sensory, best language, dysarthria and extinction and inattention; each one with ratings scored with three to five grades, being zero the normal value[37, 38].

Barthel Index aims to evaluate functional potential of patients. Thus, it uses 10 items to measure daily living activities and mobility, like feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers (bed to chair and back), mobility (on level surfaces) and stairs. Using this index, it is possible to determine the baseline level of functioning and monitoring of activities over the time. The index assesses what a patient really does, not what the patient could do. To assess independence of activities, the total scores range from zero to one hundred, representing lower scores increased disability[39].

These three scales were used in some clinical trials as inclusion and exclusion criteria or even to assess state and progression of patient's health over the time. Thus, the understanding of these tools is essential to conduct clinical trials in neurology, giving me ability to participate in recruitment processes and interpretation of the health statues and evolution. So mRS, NIHSS and Barthel Index accompanied me throughout the training.

4.2. Regulations and legislation

As stated above, my internship was mainly focused on clinical trials, which are extremely regulated to accomplish quality, efficacy, safety and ethical patterns.

National and international regulations and legislation intend to ensure the respect for human dignity and fundamental rights. The rights and well-being of the participants in the clinical trials must always prevail over the interests of science and society[31].

Even though my internship did not involve a previous training in regulations, most of this knowledge was acquired throughout academic formation and it was recorded during all clinical trials activities, particularly:

- ICH GCP – Guideline for Good Clinical Practice: an international standard to ensure GCP for designing, conducting, recording and reporting trials involving human beings[26];
- Directive no 2001/20/EC of 4 April 2001: aims to guarantee the implementation of GCP in clinical trials conduction on medical products for human use[40];

- Directive no 2005/28/EC of 8 April 2005: establishes principles and details guidelines related with GCP and requirements for authorization of the manufacturing or importation of IP for human use[41];
- Law no 46/2004, of August 19th: consists in a transposition into national law of Directive no 2001/20/EC[31];
- Decree-Law no 102/2007, of April 2nd: consists in a transposition into internal legal order of Directive no 2005/28/EC[42];
- Law no 67/98, of October 26th: law on personal data protection, which is a transposition into Portuguese law of Directive no 95/46/CE of 24th October 1995[43];
- Declaration of Helsinki: define ethical principles for medical research involving human patients[21].

All guidelines provided by entities, such as EMA, FDA and ICH are also important guides for clinical development of new drugs.

4.3. Clinical trials coordination

Implementation and conduction of clinical trials involve a wide range of tasks and processes. Previous to conduction of clinical trials, they must be submitted to RA. After approval and preparation of the study and documents, trial initiation visit can be performed.

During my training in the neurology service of CHEDV, I actively participated in coordination of six clinical trials:

- **ICTUS** – International Citicoline Trial on Acute Stroke (phase III);
- **MACSI** – Membrane-Activated Chelator Stroke Intervention (phase III);
- **CAROLINA** – CARdiOvascular safety of LINAgliptin versus glimepiride in patients with type II diabetes mellitus at high cardiovascular risk (phase III);
- **SP0993 –** Study comparing the efficacy and safety of lacosamide to controlled release carbamazepine, used as monotherapy in subjects (≥16 anos) newly recently diagnosed with epilepsy and experiencing partial onset or recently generalized tonic-clinic seizures (phase III).

- **SP0994 –** A multicenter, double-blind, double-dummy, follow-up study evaluating the long-term safety of lacosamide (200 to 600 mg/day) used as monotherapy in subjects with partial-onset or generalized tonic-clonic seizures ≥ 16 years of age coming from the SP0993 study.
- **CL2-38093-012 –** Efficacy and safety of 3 doses of S38093 (2,5 and 20 mg/day) versus placebo, in co-administration with donepezil. A 24-week international, multicentre, randomized, double-blind, placebo-controlled phase IIb study.

The following topics briefly describe the clinical trials activities and my tasks and experiences.

4.3.1. Assessment of new clinical trials and pre-trial visits

The sponsor or Contract Research Organization (CRO) responsible for the study choose the investigation sites that appear to be most suitable for conducting the study and then, usually propose it to service director or principal investigator (PI). New clinical trials need to be suggested to the service and assessed previous its initiation.

Sometimes, monitors contacted me to propose new clinical trials and then I transmitted that to PI or service director. Initially, PI had access to limited study information, because sponsor/CRO firstly analyzed site's conditions and availability to perform the study. If the site was prepared and available to conduct the study, there were several steps to follow to obtain study approval and perform initiation visit.

During my internship, I participated successfully in the assessment of three new clinical trials.

4.3.1.1. Confidentiality agreement

Preparation of the new study involved the signing of confidentiality agreement, also called non-disclosure agreement, which is a legal contract established between the potential PIs and monitors of the study. The agreements were signed and dated in order to guarantee that these two parties agree not to disclose information addressed in the agreement.

Usually after PI signing that, I sent the confidentiality agreements to monitors by email, fax or courier (depending of the monitor instructions).

4.3.1.2. Site´s conditions assessment

Site´s conditions were assessed through feasibility questionnaires, usually completed by the PI (and when necessary with my collaboration). These questionnaires are used to evaluate the potential sites and investigators and select them. It contemplates the collection of information about the experience of the site in clinical trials, target disease and patient's recruitment, facilities, human and material resources and investigators. PI was also invited to fill a database, which intended to evaluate the availability of patients with target disease and the potential of the hospital to recruit patients and conduct the study. I was responsible to fill in this database. In these two situations, documents were sent back by me to the Sponsor/CRO. A feedback was also expected and often new information was asked. It was important be quick in the reply, so I maintained regularly the contact with the PI to accelerate that. Whenever the absence of any material was detected, I requested it. Commonly, missing equipments were thermometers, balances and electrocardiogram (ECG) machines.

Usually, assessment of site´s conditions also involved face-to-face visits – selection visits – which are used to present the hospital to the Sponsor/CRO, assess facilities, resources and equipments and guarantee compliance with GCP. During these visits, study protocol can be presented; investigators can provide inputs and clarify doubts; and confidentiality agreements can be signed. I had not the opportunity to collaborate in a face-to-face visit.

4.3.1.3. Financial contracts analysis

Financial contract is another aspect that must be discussed before study approval. I received financial contracts by email or courier to analyze together with PI service director. We discussed and reviewed the main points of the document, including number of patients that we were expecting to recruit (realist forecast), costs per visits/procedures and per patient recruited and approval timings by the AB and Ethics Committee (EC), among others. Generally, we used examples of other approved financial contracts to compare and avoid mistakes. Our proposals were always presented to the AB and inputs were added to the document. Then, it was sent to monitors and after being accepted, the contracts contemplating our amendments were submitted to the AB and EC.

4.3.1.4. Clinical trials approval

When financial contracts were finally rectified and the study approved by RA – INFARMED, CEIC and National Data Protection Committee (CNPD) – began the preparation of the clinical trial submission to the AB. This phase involved the collection of several documents and signatures, as:

- *Curriculum vitae* (CV) of the PI (dated and signed);
- Three copies of the financial contract signed and dated by the Sponsor/CRO and PI;
- Another documents requested by the Sponsor/CRO, AB or EC.

These documents, together with identification and CV of the sponsor, study protocol, study synopsis, informed consent, study approval by RAs, insurance certificate, clinical agreement and study authorization of the service director, were part of the submission dossier, which was handled to the AB to obtain study approval in the hospital.

This phase took around two or three months and during this period, I was contacted by sponsor/CRO to clarify some questions. All efforts were done to solve quickly all doubts.

After receiving the favorable decision of the AB, I contacted sponsor/CRO to inform them and a copy of the financial contract was sent and stored by each one of the parties involved in the procedure (AB, sponsor/CRO and PI). The copy of the PI was stored by me in the investigator's dossier.

4.3.2. Investigator´s meeting

Investigator's meeting is a conference organized by the sponsor to enhance communication among sponsor, investigators, monitors, Clinical Research Associate (CRA), SCs and other members of the enterprises, like quality assurance and project managers. Typically, these working sessions have a central location and in international trials, the meetings location can vary among the diversified countries. The main purpose of these sessions is to promote uniformity in compliance with the protocol and practices among sites.

I had the opportunity to attend one investigator meeting. In this meeting was reviewed the protocol, emphasizing inclusion and exclusion criteria, study design, deadlines, procedures, recruitment difficulties, safety concerns, how to report AEs and serious adverse events (SAE), among other specific information. Since this study implied the application of several scales to

evaluate mental patients status, the meeting also involved the explanation of scales and how to use it.

This was an opportunity to involve team members in the study, clarify doubts about the protocol and procedures and establish professional relationships and peers networks. After the meeting, I felt me more able to initiate the study.

4.3.3. Clinical trial initiation visit

Clinical trial initiation visit represents the official beginning of a clinical trial and aims to finalize the preparation of the study and ensure proper conditions study conduction. This visit involves a meeting with investigators, SC, pharmacists and remaining investigation team. During my training, I performed one of these visits.

Firstly, I scheduled an appropriate date to this meeting with monitors/CRA and investigation team. Until the visit, I maintained the regular contact with the monitor/CRA and various documents (CVs of the investigation team, including nurses, pharmacists and mine, signature of the protocol, disclosure agreement, among others) were being prepared and signed, as well as some of the study trainings were completed, passwords checked and archived into a file. I also read the protocol and other relevant documents. Previous preparation allowed streamlining the scheduled meeting.

Initiation visit was the first moment that all team members had contact with the clinical trial and procedures involved and had opportunity to discuss (and receive training, if applicable) about several aspects, such as: study protocol, synopsis, informed consent, investigator brochure, inclusion and exclusion criteria, AE, SAEs, study duration, administration of the medication, case report form (CRF), collection of biological samples and medical procedures, equipments, GCPs, monitoring visits, inspections and audits. In the pharmacy, all pharmaceutical practices and procedures were also explained and discussed. It was important to clarify all doubts. At the end of the presentation, team members signed multiple documents, as delegation signature log, visit log, training certificates and other essential documents, which individually or collectively contribute to the evaluation of study conduction and data collection[26].

After that, the visit continued with monitors/CRA and me. This step involved to check the place where the study material was arranged, laboratory kits (expiration date and missing kits), operation of the equipment (thermometer, ECG machine) and Investigator Site Files (ISF). I also

received training about subject's diaries and cards, randomization, medication assignment, report of AEs and SAEs, CRFs, source documents, laboratorial procedures and shipment of samples. All passwords (to access to e-CRF, interactive voice response system (IVRS) and interactive web response system (IWRS), among others) were confirmed. To finish the visit, I helped the monitor/CRA in the organization of the documents into the ISF. Site became ready to initiate recruitment of patients.

4.3.4. Recruitment period

Recruitment period is the time during which investigators have the opportunity to recruit its patients share for the study[44]. This period, as well as the expected number of patients to recruit, is specific for each clinical trial and site. PI and sponsor/CRO are responsible to determine the number of patients to recruit for each site, but there are several aspects that influence the recruitment. Duration of recruitment is one of these factors, because lengthy recruitment periods allow recruit more patients and vice-versa[44]. Target disease makes vary the number of patients available to engage in the study and time needed to achieve the intended objectives. So, validation of feasibility questionnaires influences the recruitment compromise, estimating number of patients with a specific disease available in a timeframe[44]. Sample size is determined before the study initiation in order to guarantee statistical power of clinical trials results[44]. However, during the studies, are often performed interim analyses that allow extend or limit recruitment. Any update in recruitment compromise is communicated to the investigation team.

Depending of the studies, eligible patients were detected in the emergency service, internment and external consultations. Furthermore, in some studies, it was possible to look for eligible patients in patient's databases.

My contribution to the recruitment was mainly related with search of patients in databases. In the hospital, there were several patient's databases, organized by diseases and including diversified variables, such as concomitant diseases, age, and gender. Considering one or two inclusion criteria, I made pre-selections of patients. Then, through the hospital platform, which provides an integrated view of clinical information related with patients to healthcare professionals – medtrix – and clinical processes, I verified clinical data of the patients and compared that with eligibility criteria. This procedure was repeated using few databases. Contacting patients by phone was the next step to arrange a visit with the available pre-selected patients.

If Investigators selected a potential candidate to pre-screen, I was informed. Usually, the physician gave me the name and/or the process number of the candidate to confirm criteria and then, I contacted him and arranged a visit.

Whenever a potential participant to a clinical trial was recruited, investigators and I were responsible to verify compliance with inclusion criteria and non-compliance with exclusion criteria and all study procedures, advantages, disadvantages and other relevant information were explained to patients by the investigators. Patients also had time for questions and took a free and informed decision. I verified all informed consents to avoid errors in this procedure.

Throughout the study, I regularly recalled the investigation team about the recruitment closure approach, to avoid non-inclusion of eligible patients.

4.3.5. Randomization of patients

Randomization can be defined as the process of allocate a population sample into groups that will receive distinct interventions: test or control treatments. This method avoids systematic differences (known and unknown baseline variables) between groups that could influence study outcomes and empowers statistical inferences. If studies don't follow a concurrent randomized control, biases are not eliminated and study results may not be reliable[45].

There are several types of randomization and patients can be allocated in different groups or study arms. These characteristics are defined in the protocol of each study. In clinical research sites, randomization can be done through two systems: IVRS or IWRS. These systems are cost-effective solutions to randomize patients and are available every day of the week, during 24 hours. I had my own passwords to access to these platforms and randomize patients. After that, the system assigned to each participant a medication number and, in some cases, it was also assigned patient's identification numbers. Confirmation of the randomizations and assigned codes were sent to my email. I printed, requested investigator signature and indexed it to patient´s worksheets.

IVRS/IWRS were also used with other functions, such as: recording failures in the patient's screening, obtaining subsequent drug assignment or a replacement kit, dose titration, discontinuing a patient, acknowledging study drug receipt, registration of an unscheduled visit, completion of a patient, resolution of temperature excursion and restarting a patient drug.

4.3.6. Clinical visits

This period of clinical trials encompassed all activities related with patients, including preparation and conduction of the visits.

Before these activities, I reviewed visits plans to obtain a broad overview of the status of patient in the trial and organize the visit.

4.3.6.1. Scheduled of visits – visit appointment

Visit appointment comprised call to patients to dial, redial and/or remind them about a visit. Generally, I called patients few days before the visit to appoint a new visit or to remind them about appointed visits. During this call, some information was usually communicated:

- Date and time of the visit;
- Need to bring patient diaries and unused study medication, as well as packaging of used medication (if applicable);
- Need to be fasted (if applicable);
- Other specific procedures.

When it was impossible contact patients by telephone, I sent a letter contemplating the same information. All visits were registered in the hospital informatics system.

The management of patient's visits of the several clinical trials was a complex task. In order to facilitate it and avoid mistakes, I elaborated and upgraded regularly excel tables with the scheduling of patient's visits by study, according to the deadlines established in the protocol. Every week, I verified in these tables the scheduled visits to the next days.

4.3.6.2. Preparation of the visit

Each clinical visit should be previously prepared to guarantee compliance with all required procedures. Usually, preparation was carried out one or two days before the visit.

Study flowchart and visit plan (included in some study dossiers) resume procedures involved in each visit. Thus, I used these resources to check required procedures and prepare all essential materials, such as:

- Patient's clinical records;
- Patient's dossiers and/or CRFs;
- Laboratory kits;
- Pharmacy prescription form;
- Materials for biological samples shipment (ambient temperature and/or dry ice).

Laboratory kits preparation involved the identification of laboratory tubes and completion of requisition forms with patient's identification number, date of birth, visit date and number of the visit (if applicable).

For each visit, I also prepared patient dossier or CRF (if applicable) and clinical process. To facilitate study conduction, I schematized and delivered a list with visit procedures to the investigator. Sometimes, I made a prevision of the procedure's duration to inform investigators.

4.3.6.3. Visits

Each study was composed by specific visits with variable procedures according to pathology, study phase, visit number and concomitant diseases and therapeutics. However, there were a set of procedures generally common to the most of the visits, such as: reception of the unused medication and medication packaging (even if empty), drug accountability, measurement of vital signs, collection of biological samples (blood and urine), ECG performance, revision of inclusion and exclusion criteria, report of AEs, verification of concomitant therapy, IVRS/IWRS contact, and patient counseling.

Often flowcharts defined tasks order and timings to perform that. These indications should be strictly complied.

When patients arrived at the hospital, I was responsible to forward them to a medical office or day hospital. Firstly, I received the returned mediation and packaging and carried out drug accountability, which was recorded in the worksheets or CRF (number of pills used and returned and number of pills that should have been taken). It allowed calculate patient's compliance with the study medication. Non-compliance could lead to patient exclusion of the trial. In cases of intravenous IP, accountability of the medication containers was also performed. In both cases, returned medication was delivered in the pharmacy (responsible for the receipt, dispensing and storage IP), where accountability was also required and recorded by the pharmaceutical.

Usually, vital signs (blood pressure, pulse rate, temperature and respiratory rate) were measured and recorded, as well as, if mandatory, ECG should be performed. I helped investigators to prepare the materials, measure vital signs and record that. I learned how to operate with an ECG machine and after the exam, I was responsible to send the ECG to a defined central lab, which generated a report. I printed and archived that in patient´s dossiers or CRF after investigator validation.

Collection of biological samples was done by the investigator or a nurse. Once again, I prepared the materials (note that laboratory tubes identification was previously carried out) and aided during the performance of that tasks, which also involved record date and time of the collection .

Revision and record of physical examination (may include evaluation of mRS, NIHSS and barthel index), AEs, concomitant medication, inclusion and exclusion criteria and patient counseling were duties of the investigator and me.

If the visit required IP dispense, I requested medication assignment through IVRS/IWRS. Usually, I preferred use IWRS. So using a computer, the subsequent drug assignment was selected and medication number assigned. Pharmacy prescription drug was filled by me and signed by the investigator. Next, this was delivered in the pharmacy and signed, dated and achieved in the portfolio of the clinical trial by the pharmaceutical. The IP was dispensed. Investigator and I handed it and reminded patient about instructions of use, as well as the need of devolve unused medication in the next visit. If the first dose of the drug was administered in the hospital, date and time of administration was recorded. The confirmation was recorded together with patient worksheets.

At the end of the visit, I received patient´s bills and reimbursed previous visit´s expenses.

In addition, there were also visits that included cognitive functions tests and depression assessment. I aided investigator or the neuropsychologist in patient´s assessment, application of questionnaires and data recording.

Screening visits were notably different from the others, since these visits were targeted to include new patients in trials. As stated above, investigator explained to patients all study procedures, with opportunity to clarify doubts and subsequent signature of the informed consent. I was responsible to verify if everything was alright. In this phase, it was essential review inclusion and exclusion criteria. Other procedures, such as physical examination, vital signs or collection of biological samples, could or not be required.

The subsequent visits could also imply signature of the informed consent, if an amendment was approved. Thus, all new patients recruited signed the new consent (substituted in the dossiers) in the screening visit, while all still enrolled patients were invited to re-sign the informed consent in the next visit, after a briefly description of the amendment.

4.3.6.4. Processing, packaging and sending biological samples

After visits, biological samples needed to be processed according to the protocol indications. Thus, samples were sent to a central laboratory previously defined and responsible to analyze them.

Usually, I granted approximately 30 minutes to clot the blood samples and when necessary, tubes were centrifuged (centrifugation time and rotations were specified in the protocol). After that, I transferred the serum to the transfer tubes. Urine samples were transferred from the urine collection vial to the transfer tubes. After that, requisition forms were completed with collection times and a copy of that attached into patient´s dossiers or CRFs.

Some of the blood samples needed to be packed and sent to the central lab in the same day of the visit at ambient temperature, while other samples were frozen in the freezer of the laboratory of the hospital and sent to the central lab in a maximum of a month. To send the samples, I called to the indicated carrier to arrange transportation. The frozen samples were shipped on dry ice. So previous to transportation scheduled, it was necessary request dry ice to storage the samples and then sent the frozen samples.

When clinical analyzes results were available, that information was sent for me through fax or email. I printed and attached it to patient's worksheets in the dossier or CRF after investigator validation. I carefully managed all these procedures to avoid any problem or error that could affect conduction or maintenance of the patients in the study.

4.3.6.5. Documents, CRFs , AEs and SAEs report

After the visit, I also reviewed all source documents and new data generated to guarantee that no errors were registered in the patient's dossiers or CFRs. Then if applicable, that information was introduced on the e-CRF. If any information was not totally clarified or there was missing data, it was annotated and enlightened with the investigator. All information should be correctly filled.

In case of AEs and SAEs report, these were reviewed and monitored adequately and patient´s follow-up was performed as necessary. SAEs were sent to the monitors of the study within 24 hours after being detected with the maximum of information.

4.3.6.6. Other activities performed after the visits

The data introduced into the e-CRF were always reviewed by monitor/CRA of the study and any discrepancy was sent to me through the e-CRF platform, email or fax. Queries were answered by me and if necessary, investigator support was requested to guarantee reliability. When queries were sent through e-CRF platform, I submitted it after answered. When queries were sent by email or fax, I printed that and after answered, it needed to be validated by the investigators previous to give it back.

Additionally, I also communicated with monitor/CRA and helped them solving and updating clinical trials issues. All correspondence, newsletters, emails and other study information was received and archived in the correct dossiers. If necessary, new information was communicated to investigation team. I tried to solve all issues as soon as possible, preferably “in real-time”.

Beyond interaction with monitor/CRA, the frequent relationship with investigation team was essential to maintain team members updated, focused on their duties, problems resolution and difficulties overcome.

I organized all study materials, including patient’s dossiers, ISFs, laboratorial kits, shipment containers of biological samples, ECG machines and other materials of each study. Regularly, I checked the stock of materials and laboratory kits in order to verify availability and validity. If materials or expiration date were running out, I asked the replacement to monitor/CRA. When new materials arrived to the hospital, they were stowed on the right places.

Once freezer temperatures needed satisfy protocol indications, when samples were frozen in the hospital laboratory, I verified regularly temperatures and recorded that in the temperature log.

Some problems were detected when the first samples were stored in the freezer, since the laboratory had no records of thermometer calibration and temperature records obtained were not correct. So, it was necessary request new thermometers, to register the calibration and then record correctly freezer temperatures.

4.3.7. Patient´s discontinuation

Patients included in the clinical trials were regularly evaluated to guarantee patient´s safety and adequate conduction of the study. Non compliance with the clinical trials deadlines and safety problems were the main reasons to discontinue patients of the studies.

After detected a discontinuation reason, the investigator communicated immediately to patient their trial exclusion. The reasons were explained to patient and described in the clinical process and CRF/patient dossier. On the other hand, if patient missed to a visit, I called him to determine the reasons and if required, to communicate exclusion of the trial. In both cases, if discontinuation was confirmed, I tried to arrange with patient an acceptable date to make the last study visit and recover study medication and materials. In these cases, I was responsible to verify the information recorded, discontinue patient through the IVRS/IWRS and introduce new data into the e-CRFs (if applicable). If any additional intervention was also required, it was recorded and followed.

The patient´s discontinuation was always communicated to sponsor/CRO and monitors and if discontinuation occurred due to safety concerns, AEs were notified.

4.3.8. Monitoring visits

Monitoring visits are performed by qualified monitors (with scientific and clinical knowledge and adequately trained) nominated to the sponsor of each study to guarantee:

- Protection of rights and well-being of human subjects;
- Accurate, complete and verifiable reported data from sources documents;
- Compliance with protocol/amendments, GCP and regulatory requirements[26].

Monitors scheduled with me the monitoring visits, usually by telephone, to ensure my availability and the presence of the PI.

Few days before the scheduled monitoring visit, I prepared all the materials needed to the visit, as study dossiers, participant´s dossiers, CRFs, clinical processes and other source documents. These materials were organized and stored in the cabinet until the visit. Often, monitors sent to me by email a list of the dossiers and documents needed. I reviewed all documents to ensure the quality of the data and resolve outstanding issues, related with queries, AEs and/or SAEs, missing data and unintelligible data. The e-CRFs were also checked and completed, if any information was

missing, as well as the follow-up letter of last monitoring visit was checked to confirm the accomplishment of these topics. Some of these issues needed to be discussed with the investigators. If any doubt or outstanding issue persisted, I appointed that to resolve with the monitor in the visit day.

During the visit, monitors analyzed all documents and I had the opportunity to observe their work and then helped with the reading and comprehension of source documents, clarifying issues and expressions and solving outstanding issues. If possible and to obtain the maximum advantages of the visit, I tried to solve all issues detected “in real-time”. When some questions needed collaboration of the investigators, it was possible to get together with investigator and solve that also “in real-time”. On the other hand, there were other issues unable to solve immediately. So, I appointed that to resolve later. Few days after the visit, monitors also sent a follow-up letter of the visit, including a description of the monitoring and outstanding issues.

The management of patient’ expenditures was also performed in the monitoring visits. I delivered to monitors travel bills of the last patient’s visits and I received reimbursement of the other visits to devolve to patients.

Sometimes monitors visited the clinical service, the pharmacy and the clinical laboratory to check the availability of all conditions required to the study conduction. Monitors tried to satisfy unmet needs. In the pharmacy, visit also entailed monitoring the dossiers and confirmation of drug accountability.

There were some monitoring visits performed by phone, interspersed with in-person visits. These visits aimed to solve outstanding issues, so by phone it was verified, clarified and corrected information introduced. Some documents were sent by fax or email to the monitor.

In case of a study audit, which involves to evaluate trial related activities and documents[26], there will be previous monitoring visits to prepare it. Audit preparation involves review and update source documents, e-CRF and study and patient’s dossiers. Protocol and study procedures should be refreshed by the investigation team. However, during my internship, I had not the opportunity of collaborate with any audit.

Although slightly different of the monitoring visits, when recruitment was stationary, some monitors convened investigation team to refreshing meetings in the hospital. It included a briefly description of the clinical trial, inclusion and exclusion criteria and required procedures, in order to boost the study.

4.3.9. Closeout visits

Closeout visits occur after the end of recruitment period and when all patients of the study have completed the last visit. I had the opportunity to participate twice in closeout visits.

To closeout a study, the sponsor sent to the investigation team the end study notification. Monitors also contacted with investigation team and me to inform about that and the required procedures. Together with monitor and PI, we scheduled the closeout visit.

To prepare this visit, I completed all documents and solved all outstanding issues and queries.

In the visit day, monitors verified all the documents and ISFs. I helped monitors solving new issues and completing missing information and documents. The Delegation Log was one of the documents that needed to be signed and dated by all team members. All documents were carefully managed and organized. I returned to monitors all equipments assigned to the hospital during the trial.

I participated in a closeout visit by phone and using a website specific to this task. Basically, it entailed the same procedures, but documents verification was carried out by PI and me, while PI was on the phone.

After that, studies were officially closed and study documents were stored in the cabinet until the sponsor authorization to archive that in a dead archive.

4.3.10. Documents archiving

According to the applicable legislation, essential documents of the clinical trials should be retained for at least five years. However, sponsor could require maintenance of the documents for longer periods. It is part of the agreement between the sponsor and the PI[41].

After receiving the sponsor authorization to archive essential documents, I packed all materials into boxes and affixed a label with the retention period. Then, I contacted with the PI to notify the clinical archive of the hospital and solicit a place to store that boxes.

4.4. Observational studies coordination

Observational studies differ from clinical trials, since subjects are not submitted to any clinical intervention. Thereby, its coordination usually implies simplest visits and tasks.

During my training, my active participation in observational studies comparing with clinical trials was lower. PORTYSTROKE (follow-up) was the only observational study conducted in the neurology service over the last months. Recently, a new observational study was suggested to the service. However, until the end of my training, the study was not yet approved by the AB of the hospital.

4.4.1. Approval of observational studies and site initiation visits

During the nine months as SC in CHEDV, no observational studies were approved and/or initiated. However, according to the knowledge acquired, it is possible to assert that ethical evaluations of these studies should not be identical as those applied to clinical trials. Ethical considerations should be suitable to the type of the study, considering risks and benefits to the patients[46].

4.4.2. Conduction of observational studies

Similarly to clinical trials, the observational study in which I participated also implied the recruitment of patients and signature of the informed consent. Recruitment period, as well as the conduction of first visits and collection of initial information, had finished previous to the beginning of my internship. So, I was responsible by the conduction of the follow-up.

Follow-up involved the collection of patient related information to fill in a form about the occurrence of new vascular events (cerebral or not), evolution of the clinical and familiar history since the previous event and current status of the patient. The occurrence of events or patient's death was described in the new events form. Usually, patients were contacted by phone, which prevented their travel to the hospital. When it was impossible, questionnaires were answered in a clinical visit. Previously to the patient´s contact, I completed a database with the phone numbers of the recruited patients (available in the informatics system of the hospital). Research of most recent clinical information and patient´s age was also performed. It allowed me to adapt my speech and approach to each patient during the contact, which was indispensable to the success in data collection. All information gathered was introduced in the study database. No monitoring visits were required during this period.

4.4.3. Closeout visits

Closeout visits of an observational study will be similar to the closeout of a clinical trial. However, it will not involve reconciliation and return of unused medication. Documents will be also stored in a dead archive.

At the end of my training, the observational study was still ongoing. So, I had not the opportunity to close it out.

4.5. Information and databases organization

The organization and management of information and documents is an essential step to the success of the studies and to adequately measure safety, efficacy and quality of the interventions. So, all efforts were done to maintain documents organized and not to lose any information. At the beginning of each study, I put all study dossiers in the specific shelves of the trial and all documents, emails and information received were adequately archived in the specific sections of the files. The monitors checked files organization during monitoring visits and at the end of the trial.

In addition, databases were also important tools during the performance of the clinical trials and observational studies, mainly related with the traceability of patients. For each study approved in the neurology service of CHEDV, I created a database involving recruited patients, using the excel office. Generally, databases presented a defined structured to meet the needs of data to store and involved similar parameters, such as identification number of the patients in the study, clinical process number and name of the patients, inclusion date in the study, visits numbers and dates. Depending the studies, databases included specific parameters, as kit medication number.

I was responsible to create and update databases of the several ongoing studies and new trials. Data confidentiality was guarantee by maintaining the information flow restricted to the investigation team and the responsibility of managing the database attributed to me.

I also developed databases for each trial or project containing all access links and respective passwords of the PI and mine, related with e-CRFs, IVRX/IWRX, study portal and others.

5. Other projects and collaborations

During my training in the neurology service of CHEDV, I also participated in some projects of the service and collaborated in scientific articles. This chapter describes my activities in three projects of the service, as well as the collaboration in three scientific articles.

5.1. National System of Health Evaluation ("Sistema Nacional de Avaliação em Saúde" – SINAS) Project

SINAS is a pilot project promoted by the Health Regulator Authority – "Entidade Reguladora da Saúde" (ERS) – in 2009. This project consists in an evaluation system of services provided by various healthcare institutions, in order to assess and disclose the quality of the healthcare services. SINAS is based in standardized indicators, such as satisfaction of patients, facilities comfort, safety and waiting time. The indicators selected have high scientific evidence and were developed by the Joint Commission International. The information produced results in a simple, clear, concise and objective classification (through ratings), that assess the quality of services and is easily perceived by patients[47-49].

This project began with the evaluation of orthopedics services of NHS and private hospitals, but it is now also applied to gynecology, obstetrics, pediatrics, cardiology, outpatient surgery and neurology. Healthcare providers updated data quarterly and are responsible for the data fidelity[47, 48].

The stroke is the SINAS intervention area in neurology and it involves seven indicators:

- Prophylaxis of venous thromboembolism;
- Antithrombotic therapy prescribed at discharge;
- Anticoagulant therapy prescribed at discharge in cases of atrial fibrillation;
- Thrombolytic therapy;
- Antithrombotic therapy administered until the second day of hospitalization;
- Statin prescribed at discharge;
- Physiatric assessment[49].

Some stroke occurrences were selected from total of stroke hospitalizations following predefined criteria. On average, 15 stroke occurrences had been chosen by month. Each list was periodically sent to neurology service in order to obtain required data.

I was responsible to introduce into SINAS database the required clinical data researched in clinical processes of patients included in the listing. My internship covered two SINAS phases: the first one included a listing with 30 stroke patients referred to May and June of 2011 and the second phase embraced 90 stroke occurrences from July to December 2011. Previously, I read the manual of this quality system to be able to correctly fill the database.

5.2. Safe Implementation of Thrombolysis in International Stroke Thrombolysis Register – SITS-ISTR

Thrombolysis, also known as thrombolytic therapy, is a pharmacological treatment to dissolve (lysis) dangerous blood clots in the vessels, improving blood flow and preventing cerebral damage. Usually, this is intravenous and is used as an emergency treatment of acute ischemic strokes, in patients younger than 80 years ago and treated within 4,5 hours of onset symptoms[50-52].

Neurology service of CHEDV is participating since 2005 in SITS-ISTR, a long duration project, which involves registering thrombolysis performed in our hospital. For each procedure, it is required to complete a lot of information associated with the event, like date and time of the onset symptoms and hospital admission, medication dose, patient weight, exams performed, NIHSS in the admission and two hours, 24 hours and seven days after the treatment, type of the stroke and mRS previous to the stroke and three months after the stroke. I was responsible to collect that information. So, regularly I verified all cases of thrombolysis (in stroke patient´s listings) and then, I filled the forms with information collected from medtrix and clinical processes. In case of any doubt, I asked clarification to physicians. Information was introduced in online platform by me.

Additionally, that information was also useful to the AB to service performance in stroke treatment.

5.3. COGWEB collaboration

COGWEB is an integrated cognitive training system, developed for distance cognitive training. This system consists of a set of tools that aims to improve the ability to implement high standard cognitive training programs[53].

This system includes two major components:

- Online system: composed by twenty computer exercises, incorporated into a computerized prescribing and monitoring platform (web 2.0). Exercises are organized by cognitive domain and evolve automatically through several difficulty levels. It allows the implementation of training programs at patient's home under specialized supervision and at affordable costs;
- Complementary materials: with format of exercise books and containing traditional paper and pencil exercises, these materials are organized in daily training blocks with varying levels of difficulty. They are relevant for patients with several limitations, without regular access to computer or internet, and facilitate the development of daily-based training routines[53].

COGWEB is the first that simultaneously integrate an interactive web platform with machine learning abilities, cognitive training exercises and a database to register patient's performance. This system is structured for modular cognitive training, since exercises are grouped according to major cognitive domains stimulated and covers different degrees of impairment (from normal to moderate deficits), with sequential levels of difficulty (easy, medium and difficult), each one with sublevels. It can be easily accessed at home or in any other comfortable place in the community with an internet connection, only requiring a password and with no need for any kind of software installation[53].

This project has been developed in collaboration with CHEDV and I cooperated in small tasks, when required. This tasks involved transposition of COGWEB site contents to a word file, facilitating translation to English, preparation of some documents, contact of some healthcare professionals, among others.

5.4. Scientific articles collaboration

The opportunity of participation in scientific articles was also another learning activity carried out in my training. I contributed to three scientific articles in different levels, from collection, analyses and interpretation of data to writing the article.

5.4.1. Short report: "Freeze the stroke" – Public awareness program for immediate detection of first symptoms

Stroke is an emergent medical condition often responsible for permanent lesions and death of the patients. The ability of the general population to identify stroke signs and the need to call 112 to obtain emergency care can be a major determinant for the success of the pre-hospital emergency pathways[54]. Thereby, several efforts have been done to reduce time for hospital arrival and treatment of stroke patients.

Previous studies involving massive public information through the media were usually expensive and short lived, without consistent improvement of stroke awareness and knowledge of the general population.

An investigational team of CHEDV (composed by neurologists and nurses) developed and assessed the impact of an alternative educational strategy, focused in selection and divulgation of posters for acute stroke detection. Special subgroups, like relatives and neighbors of acute stroke patients, were the target population.

Despite not having collaborated in the development and performance of this project, I was challenged to write the short report *"Freeze the Stroke" – Public awareness program for immediate detection of first symptoms* in collaboration with Dr. Vitor Cruz. The article describes this study and compares obtained results with previous educational strategies.

I began this task reading all materials available about this strategy, including the poster handled to the relatives and neighbors of patients admitted in our unit, questions applied to assess participant knowledge, study methods and results and some presentations about this project. This allowed me to review the entire project before writing the article.

The subsequent step consisted in reading the related articles previously chosen and in researching freshly published articles related with stroke awareness and knowledge. This information was used to review what had been done so far and compare the various approaches.

Based on that data, I wrote a short report describing the purpose, methods, results, discussion and conclusion of the applied strategy and it was reviewed by Dr. Vitor Cruz and me. It was possible to conclude that our strategy was effective in increasing awareness of the special groups to the stroke warning signs and the importance to promptly activate pre-hospital stroke pathway. It constitutes a low cost, feasible and longer duration educational strategy. This work was submitted and published in the *Stroke: A journal of Cerebral Circulation* [54].

The reviewers sent to us a listing of changes and comments which were reviewed by Dr. Vitor Cruz. The short report contemplating new amendments was newly submitted to the same journal and a new small revision was again required. The short report was finally approved by the journal and published on September 2012.

5.4.2. Article: Ischemic vagus nuclei lesions and hyperglycemia – A study in 26 patients with lateral medullary infarction and matched controls

Hyperglycemia is a common event after stroke in diabetic and non-diabetic patients. Furthermore, there are evidences linking hyperglycemia with infarct expansion, worse functional outcomes and mortality. According to previous studies, lower brainstem nuclei of the vagus nerve modulate insulin secretion and these nuclei are usually injured in lateral medullary infarction. So, infarction of the insular region was related to higher glucose levels[55].

I was challenged to cooperate in data collection and review an article aimed to compare poststroke glycemic control in patients with lateral medullary infarction with other stroke patients.

Once lateral-medullar ischemic stroke presents as common and disabling symptom the dysphagia, recovery time of the patients is not well known and few survival studies published showed inconsistent results[56], I also collected data related with this symptom.

I began this mission reading some materials published about the disease to really understand it and what had been done. After that and together with Dr. Luís Ruano (neurology resident in CHEDV), we developed an appropriate follow-up questionnaire about new vascular events, survival, current disability and glycemic control. The objective was to apply the questionnaire to patients selected to this two researches by telephone. So, I inquired all patients and when it was impossible contact patients, I contacted with relatives. Missing data, specially related with

glycemic control, was collected from clinical processes. The collected data were introduced into an excel file, to facilitate statistical analyses.

After statistical analyses, Dr. Luís Ruano wrote the article "Ischemic Vagus Nuclei Lesions and Hyperglycemia: A Study in 26 Patients with Lateral Medullary Infarction and Matched Controls". I was responsible to review the article and correct some mistakes. The study seems to support that vascular lesions of the vagus nerve nuclei worsen poststroke glycemic control. So, vagus nerve has important role in modulation of pancreatic insulin secretion, as well as poststroke hyperglycemia may be associated with particular stroke locations. It is important note that the results may not be definitive and further clinical research is required[55]. The publication of the article was accepted in the Cerebrovascular Diseases – Journal, on 14th September 2012.

With collected data, it was also possible to extract information to write the abstract "Survival and prognosis in a cohort of 41 patients in lateral-medullar ischemic stroke", which was submitted and presented in the 21st European Stroke Conference, in Lisbon, Portugal. According to the results obtained, mortality was specially high in the first months and declined after that. The symptom dysphagia persisted for more than 2 months in most of the patients. However, survivors had a good functional outcome[56]. Hereafter, it will be developed an article about this theme.

5.4.3. Article: A novel movement quantification system capable of automatic evaluation of upper limb motor function after neurological injury: Proof-of-concept

The article *"A movement quantification system capable of automatic evaluation of upper limb motor function after neurological injury: Proof-of-concept"* consists in the description of a study conducted to develop and preliminarily validate a system able to perform automatic, precise and rapid evaluations of motor functions of patients and its implementation in an ordinary clinical environment.

The objective of the authors was to publish that in the *Neurorehabilitation & Neural Repair – An International Journal of Translational Science for Researchers and Clinicians*. My small contribution in this manuscript was related with the adaptation of the article to the format style of the journal. The possible changes were made immediately by me and then, I elaborated a change´s listing to the authors, contemplating aspects to review.

6. Validation of the questionnaire: “The Cambridge Pulmonary Hypertension Outcome Review” (CAMPHOR) for Portuguese population

During my training, the Secção Autónoma das Ciências da Saúde (SACS), UA, which is the sponsor of the observational study SACS-01, invited me to collaborate in the validation of the CAMPHOR questionnaire. This task was independent of the training in CHEDV and it was performed in the Hospital Santo António, which is part of the Centro Hospitalar do Porto, together with Hospital Maria Pia and Maternidade Júlio Dinis[57].

The primary objectives of the study SACS-01 – “Assessment of the functioning, disability, quality of life and depressive symptoms in patients with pulmonary arterial hypertension” are validate the CAMPHOR for Portuguese population and assess the functioning and disability of pulmonary arterial hypertension patients through a questionnaire of 36 items “WHO Disability Assessment Schedule II” (WHODAS 2.0). I was responsible to face-to-face interview of ten patients, with different education backgrounds, social levels and age, in order to assess the relevance, acceptability, comprehensiveness and understandability of questionnaire items in Portugal. Firstly, I inquired patients about their birth date, quality of life, education level and stage of disease. After that, the questionnaire was applied to the patient and I clarified any doubt presented by each patient, while observed the questionnaire resolution and noted patient´s reactions. At the end, I asked their opinion about the questionnaire (if any information was missing or inappropriate). This mission was complete in three days.

7. Discussion

This chapter discourses about my nine months internship as SC, as well as some competences and skills acquired over that time; however, it was extremely difficulty to describe this unique experience, almost indescribable.

As stated in chapter 2, the neurology service of CHEDV does not have a clinical research office, as well as human resources skilled to coordinate studies. It constitutes the first and bigger difficulty of my training. Therefore, it was essential to understand hospital's organization and be aware of how SC functions could improve clinical research of the service. Abilities of integration and adaptation to new situations and variable teams were tested and developed during this experience.

In spite of the availability and motivation of Dr. Vitor Cruz and other investigation team members to support my work and clarify my doubts, moments of doubt, "loneliness" and even the "feeling of being lost" were unavoidable. However, these were also useful times to learn how to deal with unknown and unexpected situations and solve these issues. Integration in cross sectional teams helped me to overcome most of the challenges and look for the best practices.

According to the current clinical investigation course, the Western Europe is losing competitiveness to third world countries due to high bureaucracy, long study approval times and low recruitment rates[33]. The low approval times by the AB of the hospital improves competitive position of the site in the market. However, it still can be improved. Furthermore, the service is composed by investigators highly motivated to contribute to clinical research, interested in participate in clinical trials and focused in good recruitment rates. Site ability to recruit is one of the crucial features to the success of the clinical research. My SC functions were useful to carry out the coordination of the studies in "real time", support investigator work and improve recruitment strategies. New strategies were developed and the results were positive – recruitment goals accomplished.

During my internship, I had the opportunity to learn and practice SC activities, as well as consolidate the knowledge acquired throughout the academy, which included legislation, GCP, ethical procedures, compliance with the protocol and guarantee of patient´s safety and well-being. I experienced all steps of the clinical trials, including study proposal to the service, submission to the AB, investigator meeting and initiation, conduction and closeout of a study.

Experience in observational studies, long-term projects and medical writing was also an amazing opportunity.

During this nine-month experience, I had the opportunity to work with different diseases and types of protocols, including distinct study designs and procedures. Contact with pathologies, like stroke, diabetes, Alzheimer disease, epilepsy and lateral medullary infarction, was useful to remind, learn and consolidate my background knowledge about this medical areas and therapeutics associated.

The preparation and conduction of a clinical trial was very interesting and what initially seemed to be a monotonous task proved to be a surprise. Each investigator had its own way of working and new situations and doubts appeared and had to be quickly solved. Each study and visit was carefully prepared, ensuring that every procedure was considered, timings were obeyed and investigation team was ready to the tasks. It implied plan the visits ahead and establish good communication flows. Planning all activities was a good option to act quickly and discern the importance and immediate priority of the activities. Verification of collection of all information was one of my functions, because everything should be recorded, since this is the only way to prove that it exists. Organization of the source documents was a hard, but essential task to protect and maintain data updated.

When I initiated my SC functions, there were several new tasks that I had to learn and practice, which include handling of samples, performing ECGs and measuring vital signs. Handling biological samples implied follow carefully the protocol. Samples identification was a crucial step so, I chose prepare that previously avoiding mistakes. In the laboratory, centrifugation and samples transference was a rigorous work, since any deviation to the protocol could comprise results and patient´s safety. The contact with patients, which also involved measure vital signs and perform ECGs, was a hard and crucial activity for me. Although I already knew that my training in study coordination would demand interaction with patients, I confess that I was not ready for that and uncomfortable feelings were unavoidable. Often, these feelings resulted from the duty to deal with patients with chronic diseases, physical and psychologically debilitated, with economic difficulties and alone. It affected me, but patients are priority in studies, their safety and welfare needs to be guarantee and my work was essential for that. So, my strategy was to provide the maximum comfort to patients, talk with them during visits and be able to listen their problems and outbursts. To implement these measures, I observed the interaction of physicians and

patients and all over the time, I improved my relationship with patients. Currently, the relation is not perfect, but is getting better.

However, not everything was bad in the relation with patients. I was able to create a relation with patients, know him/her and understand some details of their lives important to the trials. So, with practice I was able to overpass this difficulty and it became a pleasant moment. A similar situation happened with phone contact of patients, because beyond the collection of study information, I felt patient´s loneliness and the importance of "nice words" in their lives. Moreover, some patients showed their enthusiasm to contribute to medicine advances, which was rewarding for me.

Patient´s interaction (in person or by phone), as well as investigation team interface, allowed me also develop and practice communication skills, which included be a good listener, have good arguments, persuasion abilities and sympathy. It facilitated my relationships and professional performance.

One of my objectives was to quickly introduce data into the e-CRF. Preferably this task was performed after the visit and shipment of samples. It increased competiveness of our site and avoided lost of information. For me, this was much more than a data entry function, because it demanded remind, learn and think about medical knowledge. Here, the major difficulty was to comprehend medical letter. Currently, this is still a problem. So, my suggestion is to promote electronic records.

In order to improve organization of site activities, I tried to analyze and establish the best days for each investigator perform patient´s visits. In this way, I could avoid overlapping of visits. It was important, because I could not accompany more than one visit at the same time and sometimes, rooms were busy. The lack of space and impossibility to distribute attention to everyone at the same time delayed patient´s consultations.

Study medication also led to some problems. An error in the allocation of the medication to our site conducted to the assignment of wrong medication kit number by the IVRS/IWRS. This problem needed to be solved immediately, since patient was waiting for study medication. Monitor/CRA was contacted to reorganize medication allocated to the hospital. Problems with delays in medication delivered (uncomfortable issue for patients) were mitigated with a new strategy. Every time that I got a new medication kit, I informed the responsible pharmacist about the next week visits scheduled that implied waiver of medication. Thereby, my visits to the pharmacy ceased to be a surprise. On the other hand, I proposed the inclusion and training of

more pharmacists in each study to avoid non-delivered of medication by staff absence. These were two useful actions to avoid pitfalls and reduce medication dispensing time.

Sending ECGs was a common trouble in some studies, because ECGs needed to be sent by fax and hospital fax lines had no direct connection to the outside, which prevents transmission of ECGs. Once it was impossible unlock the fax line, it entailed the development of two strategies: sending ECGs by fax at home and sending ECGs through a web platform. These two strategies were used, but using a web platform was the most comfortable option after changing material. Deal with diversified problems, forced me to learn how to overtake unexpected situations and manage stress.

Monitoring visits were a surprise for me, because I had no idea about the performance of these activities. Beyond acquiring experience about accompanying of monitoring visits, I had the chance to contact with monitors of several studies with distinct backgrounds, which allowed me share experiences and learn much more. So, I also used these visits to analyze how to perform monitors work and with help of a monitor, I performed some of the tasks, including source data verification, analysis of any protocol deviation and assurance of rights, safety and well-being of patients. This was an amazing chance to learn about other working areas. Monitoring visits were scheduled beforehand, in order to guarantee my availability to accompanied monitors and the presence of the PI. On the other hand, I scheduled monitoring visits in distinct days to avoid overlapping, because I had lack of space and attention to everyone.

Sometimes, patient´s recruitment softened and no patient was included for long, so refreshing meetings were planned to update study information and capture investigator's attention to the trial. In some occasions, refreshing meetings were essential to the success of the study.

In these nine months, I collaborated in an observational study. This cannot be considered a "complete" experience, because I did not initiate or closeout an observational study. However, I think that it will involve similar procedures to clinical trials, but a little bit simplest (less ethical considerations, safety concerns and no drug accountability). So, I think that I am able to do that.

Conduction of studies involved the establishment of workflows with other departments of the hospital, like pharmacy, laboratory and provision. I tried to establish good communication flows to guarantee the success of the trials.

All studies, clinical or observational studies, had associated a wide range of login and passwords to access to e-CRF, study portal, ECG results, IVRS/IWRS, among others. For each study, I

developed a database with logins and passwords and with restricted access. It facilitated and accelerated the access to passwords, when necessary, and avoided losing these data. It is possible the development of databases more restricted, involving the controlled access by the investigators. However, until now, it was not necessary.

Although all the important learning and experiences acquired, I can also identify some faults. During the training, I did not collaborate in any audit. I consider that it is a negative aspect, because I realize an audit as an incredible opportunity of learn and become conscious about what we should or not do in a study, quality of our work, trial organization, compliance with protocol and legislation and future directions to follow. So, this is an opportunity to improve site performance in clinical trials. Moreover, I also became away from logistic difficulties with regard to long periods for study approval and delays in payments.

After study closeout, documents were archived into de clinical archive of the hospital. However, this was a challenging task, due to lack of space to put that. The creation of a specific space in the archive to retain that, organized by period of retention, can be a future option.

During my training, it was also possible to collaborate in other functions beyond my activities as SC, which included the SINAS, SITS, COGWEB and writing articles. It was a big contribute to increase my knowledge, especially in neurology. Obviously, I was faced with several challenges. With SINAS, it was difficult learn about the different therapeutics, its use and interpretation of medical decisions; with SITS, it was complicated search all required information and complete missing data. However, all over the time, it was remarkable the adaptation to these functions. Writing articles made me practice medical writing and training submission of articles for publication.

The ability to reconcile my training in CHEDV with Master units study, tests and projects was one of the greatest difficulties observed.

By the way, my training in CHEDV let me develop and/or ameliorate several skills:

- Comprehension of clinical research site functioning;
- Experience and autonomy in coordination of clinical trials and observational studies;
- Ability to be compliant with GCP and legislation;
- Ability to plan and organize clinical trials and observational studies;
- Selection of patients to each study;

- Accompaniment of patients;
- Consolidation and increase of medical knowledge;
- Data entry skills;
- Comprehension and “experience” of clinical trials monitoring;
- Networking with peers, investigators, monitors, other professionals and institutions;
- Ability to solve unexpected and urgent situations;
- Contact between investigation team members and sponsor/CRO and monitors/CRA;
- Organization skills;
- Communication skills;
- Medical writing skills;
- Prioritizing skills;
- Team work;
- Autonomy;
- Adaptation to different investigation teams;
- Ability of initiative;
- Critical thinking;
- Personal and professional growth.

The participation and collaboration in all activities required good time management, since the workload was variable all over these months, which entailed time adjustment. Nevertheless, I consider that this was an indispensible step to my professional life and an amazing opportunity of personal and professional growth. I hope that the contact established with different people and the network that was progressively built enables “opening of many doors” for the future.

8. Conclusion

This bridge between the university and the “real world” gave me the chance to participate not only in the coordination of studies, but also in a wide range of other projects, which allowed me this huge learning. To accept all the challenges was not always easy, but now I recognize that I developed technical, medical writing and soft skills. This way, challenges are not so scary and became opportunities.

My background knowledge was essential in this route. It gave me the *know-how* and autonomy necessary to initiate my job and overlap “loneliness” moments.

During my training, the clinical research was not a routine, but overall the workload was more intense at the morning, because temporal demands of the visit´s procedures led to the conduction of the visits in this period of the day. Patients were at the main focus of investigators and they did their best to provide innovative treatments to patients and improve their quality of life, always ensuring safety and well-being.

At the beginning of my training, one of the most difficult thing was time management. I had to adjust in my work scheduled patient´s visits, telephone calls, monitoring visits, answer to patient´s doubts, investigator´s attendance, prepare and organize study visits, managing of e-mails and other functions that were appearing. It demanded to develop my ability to prioritize tasks and make decisions. My responsibilities increased, since mistakes could compromise data, patient´s safety and their maintenance in the study. I also developed my discipline, communication skills, maturity and confidence and created networking.

A structured, experienced, trained and motivated team is able to conduct clinical trials more easily according to all requirements and achieve the objectives earlier. So, it is essential to implement well organized sites, to be successful in clinical research. Investigators of the neurology service are available and motivated to clinical research. It contributes to the national and international excellence of the site and it is valuable for enrollment in new clinical and observational studies. CHEDV (especially due to motivation and effort of investigation staff) was considered the best national site and one of the best international sites in one of the most recent clinical trial.

However, I realized that a SC properly trained in conduction of clinical trials improves site performance. In my internship, I was concerned with protocol and GCP compliance, organized and prepared study procedures and visits, managed clinical investigation and made a communication

bridge between investigation teams and sponsor/CRO and monitors/CRAs. By this way, important information was not lost, investigators duties were facilitated and increased the success of the investigations.

The SC functions were not just related with management and organization of clinical trials, but also embraced relationship with patients. Relationship with patients was one of the biggest difficulties that I had to overpass and it implied adaptation of my speech to the age, education degree and disease of each one. Currently, this relation is easier and natural and with some patients (especially with patients with more visits), it became a pleasant moment.

Most of the difficulties and challenges were verified in practical activities, like helping in processing biological samples, performing ECGs and measuring vital signs and capillary glycemia, because I had no experience or background knowledge in these areas. Usually, in clinical research these tasks are performed by SCs, so here becomes a challenge to the Pharmaceutical Biomedicine Master degree: include more practical classes about clinical trials procedures.

Considering the hospital perspective, clinical research is beneficial, not always to patients that have the opportunity to receive innovative and free therapeutics and to science progress, but also because of the economical benefits to the hospital. There are possibly a lot of savings in resources during clinical trials, like ECG machine and remaining materials, needles, syringes, blood and urine collection tubes, diabetic equipment (machines, diabetic strips, lancets and other diabetic testing supplies), infusion pumps, centrifuges, office material, among others. Sometimes, these materials are donated to the hospital after study closeout. Otherwise, AB receives monetary incentives to conduct the studies in the hospital. So, clinical research entails several benefits and it is another incentive to improve and promote clinical research in the hospital.

Writing this report was a big challenge, because it falls short of making justice to my training in the neurology service of CHEDV, since I cannot find the right words to describe the opportunity and knowledge acquired. Nonetheless, concentrating on the objectives presented in the introduction (chapter 1), I think that I fulfilled my task. Therefore, I assisted and contributed to the increase of “clinical research culture” in the neurology service of CHEDV. So, I would like to keep working as SC in this hospital and I think that I still have a lot to give.

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