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Relatório de Estágio num Centro de Investigação Clínica

Report on Training in a Clinical Research Centre

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Relatório 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 Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física e da Secção Autónoma das Ciências da Saúde da Universidade de Aveiro, e do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa.

Dedico este trabalho aos meus pais, os meus primeiros mestres. Nunca mediram esforços na realização dos meus sonhos e sempre me motivaram e incentivaram ao longo deste trabalho.

O júri

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

Professor Doutor Joaquim José Coutinho Ferreira
Professor Associado da Faculdade de Medicina da Universidade de Lisboa

Professor Doutor José Carlos Fontes das Neves Lopes
Professor Auxiliar da Universidade de Aveiro

Professor Doutor Bruno Miguel Alves Fernandes do Gago
Professor Auxiliar da Universidade de Aveiro

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Palavras-chave Ensaios Clinicos, Farmacovigilância, Gestão Cientifica, Centro de Investigação Clinica

Resumo

A crescente exigência de pesquisa científica, das agências reguladoras e a necessidade de maximizar a segurança dos participantes têm requerido uma gestão mais eficiente, capaz e precisa para realizar estudos de alta qualidade de pesquisa clínica e melhorar a competitividade neste campo. Para enfrentar este desafio, centros de pesquisa clínica tem surgido para apoiar os requisitos operacionais, metodológicos e regulamentares.

Este trabalho relata a minha experiência de Setembro 2011 a Junho de 2012 num centro de investigação clínica como coordenadora e co-monitora de ensaios clínicos e estudos observacionais na Unidade Neurológica de Investigação Clínica do Instituto de Medicina Molecular, as atividades de farmacovigilância realizados numa unidade regional do Sistema de Farmacovigilância Português e as tarefas de gestão científica desenvolvidas envolvendo estas duas unidades.

Como um estágio curricular com objetivo de colocar em prática os conceitos aprendidos no primeiro ano de mestrado em Biomedicina Farmacêutica, tive a oportunidade de experimentar diferentes papéis ligados à investigação clínica e compreender as responsabilidades e expectativas envolvidas em cada um deles.

Este estágio curricular deu-me uma visão realista de um centro de investigação clínica, bem como as interações entre os diferentes profissionais.

Keywords Clinical trials, pharmacovigilance, science management, clinical research centre.

Abstract

The growing demand of scientific research, regulatory agencies and the need to maximize participant safety have required efficient, capable and precise management to conduct high-quality clinical research studies and improve the competitiveness in this field. To face up to this challenge, clinical research centers have emerged to support the operational, methodological and regulatory requirements.

This work reports on my experience since September 2011 until June 2012 in a clinical research centre coordinating and monitoring the clinical trials in the Neurological Clinical Research Unit of Instituto de Medicina Molecular, the Pharmacovigilance activities performed in a regional unit of the Portuguese Pharmacovigilance System and the Science Management tasks developed involving these two units.

As a curricular internship aimed to put into practice the concepts learnt in the first year of master's degree in Pharmaceutical Biomedicine, I had the opportunity to experience different roles linked to the clinical research and realize the responsibilities and expectations involved in each one of them.

This curricular training provided a realistic vision of a clinical research center as well as the interactions between different professionals.

“Knowing is not enough; we must apply.
Willing is not enough; we must do.”
- Goethe

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AB	Administration Board
ADR	Adverse Drug Reaction
AIDFM	Associação para a Investigação e Desenvolvimento da Faculdade de Medicina (Association for Research and Development of the Faculty of Medicine)
CAML	Centro Académico de Medicina de Lisboa (Lisbon Academic Medical Center)
CEIC	Comissão de Ética para a Investigação Clinica (Portuguese Ethics Committee for Clinical Research)
CHLN	Centro Hospitalar Lisboa Norte (North Lisbon Hospital Centre)
CM	Clinical Monitor
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CT	Clinical Trial
e-CRF	Electronic Case Report Form
EU	European Union
DCF	Data Clarification Form
DIL	Direcção Inspecção e Licenciamento (Inspection and Licensing Department)
EC	Ethics Committee for Health
FCT	Fundação para Ciência e Tecnologia (Foundation for Science and

	Technology)
GCP	Good Clinical Practice
HSM	Hospital de Santa Maria (Santa Maria's Hospital)
ICF	Informed Consent Form
IMM	Instituto de Medicina Molecular (Institute of Molecular Medicine)
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde (National Authority of Medicines and Health Products)
ISF	Investigator Site File
IVRS	Interactive Voice Response System
IWRS	Interactive Web-Response System
NCRU	Neurological Clinical Research Unit
NME	New Molecular Entity
PI	Principal Investigator
RCT	Randomized Clinical Trials
SC	Study Coordinator
SPC	Summary Product Characteristics
SVIG	Sistema de Vigilância de Medicamentos de Uso Humano (Medicinal Products for Human Use Vigilance System)

Introduction

The second year curricular activities of my Master's Degree in Pharmaceutical Biomedicine were developed at the Instituto de Medicina Molecular (IMM), an Associate Laboratory located at Hospital Santa Maria (HSM) campus in Lisbon.

During this ten-month experience, I had the opportunity to be in touch with several areas related to the development of new drugs. I was actively engaged in coordinating clinical studies, co-monitoring an observational study, managing science applications with a strong component of medical writing responsibilities and participating at the Pharmacovigilance unit routine.

The aim of this internship report is to describe my training activities from September 2011 until June 2012. Figure 1 gives a time perspective of the activities performed. From September to March, I developed some activities as study coordinator of several clinical trials and observational studies. At the same time, I carried out some activities as a co-monitor of an observational study that started in October and lasted also until March. The final 3 months, from April to June, I complemented my internship with Pharmacovigilance activities. Concurrently, I was involved with a wide variety of tasks related to science management. All the activities performed during these 10 months were supervised by Professor Doutor Joaquim Ferreira, Principal Investigator at the IMM.

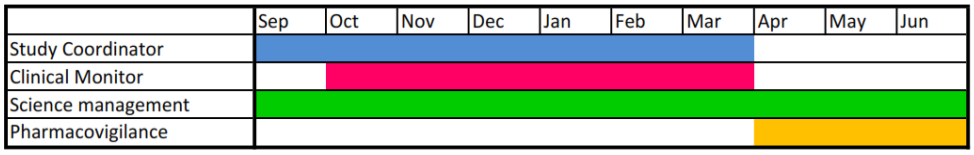


Figure 1: Temporal frames of the activities developed during my internship.

This training report includes not only the activities I performed but also my thoughts and expectations behind each learning experience of the training period.

The primary objectives I established for my internship were:

- To apply and complement the theoretical background attained during the first year

of my Master's Degree;

- To gain practical knowledge through the application of the attained skills and with the experience of senior professionals;
- To understand the multidisplinary framework of a clinical research centre;
- To obtain better understanding of the pharmaceutical research reality;
- To identify my areas of interest in pharmaceutical research interests;

This report is organized in 6 chapters: 1) Description of the Host Institution, 2) state of the art, 3) on the job training, 4) discussion, 5) conclusions and 6) bibliographic references.

The first chapter, Description of the Host Institution, describes the host institution, the vision of IMM, its privileged relations with Hospital and Medical School and the collaboration established between the 3 ones.

The second one, State of the Art of Pharmaceutical Research, gives an idea how new medicinal products are developed, the regulatory environment and the importance of a clinical research centre.

On the job training, the third chapter, reports the clinical research unit activities (study coordinating and clinical monitoring), the science management performance and Pharmacovigilance experience.

The forth chapter, Discussion, outlines the lessons learnt in the 10 months internship and the following chapter, the fifth one, Conclusions about the training.

The last one, the sixth chapter, References, lists the bibliography used as support.

1. Vision of host institution

This chapter describes the host institution's objectives, activities and structure as well as its privileged relationships with other organisations.

1.1. Instituto de Medicina Molecular

Instituto de Medicina Molecular (IMM) is an Associated Laboratory created in December 2001. It results from the association of 5 former research units from the Faculty of Medicine of the University of Lisbon (the Biology and Molecular Pathology Centre, the Lisbon Neurosciences Centre, the Microcirculation and Vascular Pathobiology Centre, the Gastroenterology Centre and the Nutrition and Metabolism Centre) and one from the Portuguese Institute of Oncology Francisco Gentil (1). The IMM´s purpose is to "foster basic, clinical and translational biomedical research with the ultimate aim of contributing to a better understanding of disease mechanisms, developing novel predictive tests, diagnostics and therapeutic approaches" (1).

Located in the campus of the Santa Maria Hospital, IMM benefits from a physical advantage to translate the clinical research achievements into clinical practice. It is mainly supported by national public and European Union funds. The research expenditure includes additional funds obtained from peer reviewed competitive grants, private donations and industrial partnerships. In 2011, the total expenditure was 10.237.384,32€ supported by several funding sources as shown in Figure 2 (2).

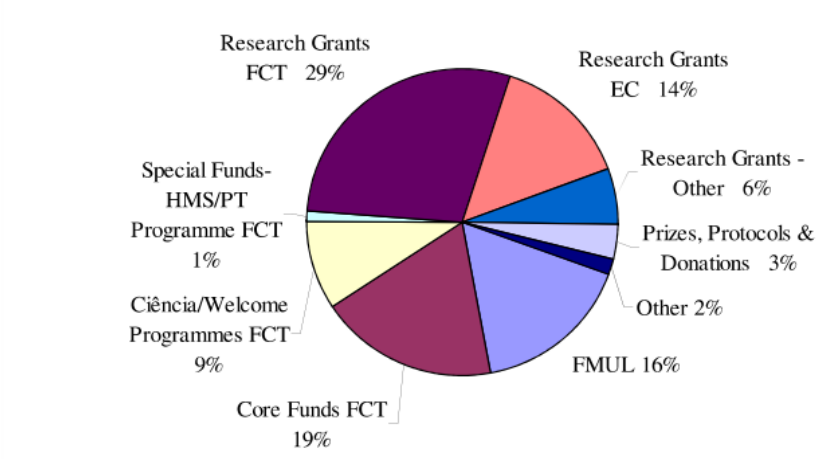


Figure 2: Expenditure in 2011 by Funding Source.

Source: Reproduced from figure in ref. 2, p. 9.

Throughout 2011, IMM has been involved in 269 research grants, promoted by several entities as shows Figure 3:

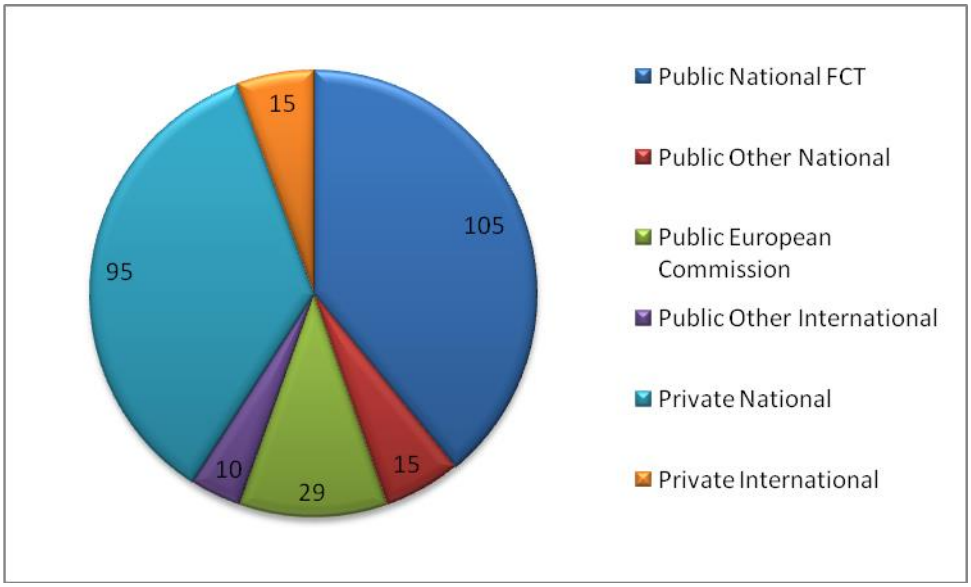


Figure 3: Number of ongoing research grants in 2011.

Source: Reproduced from figure in ref. 2, p. 9.

Historically, the IMM registered an increase in the research grants initiated, as illustrates in Figure 4:

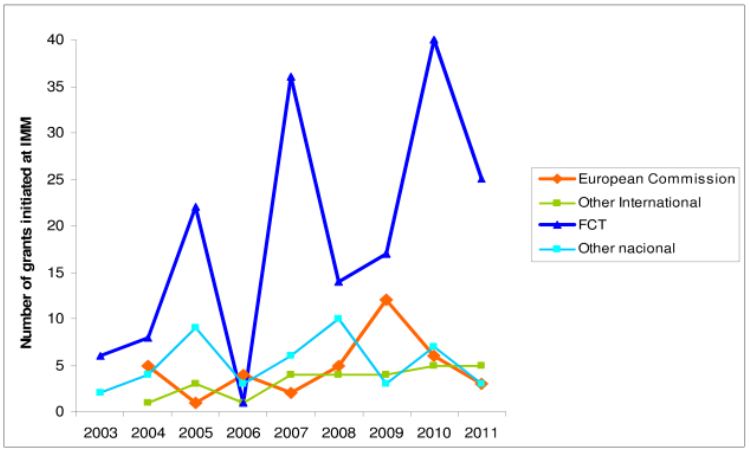
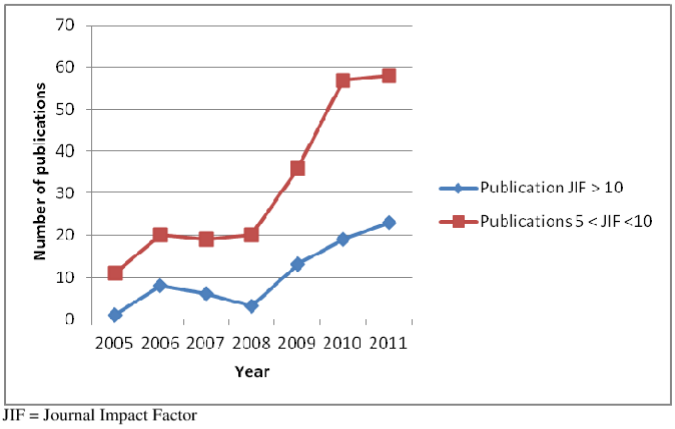


Figure 4: Number of Research Grants Initiated at IMM from 2003 to 2011.

Source: figure of ref. 2, p. 10.

As a result of an increased activity performed at IMM, it has also showed an increasing number of papers published in international journals both in journals of high impact factor (>10) as in low impact factor journals (<10) represented in Figure 5.



JIF = Journal Impact Factor

Figure 5: IMM publications in International Journals.

Source: figure of ref. 2, p.17.

At the moment, IMM hosts 31 independent research groups (about 400 researchers) that are organized in three research Programs: 1) Cell & Developmental Biology, 2) Immunology & Infection, and 3) Neurosciences. The Institute provides state-of-the-art Bioimaging, Flow Cytometry, Animal (fish and rodents), and bio-banking facilities. It also offers regular scientific seminar series by invited external speakers, and runs an international PhD and MD/PhD program with 110 students (1). The Figure 6 illustrates how IMM is organized.

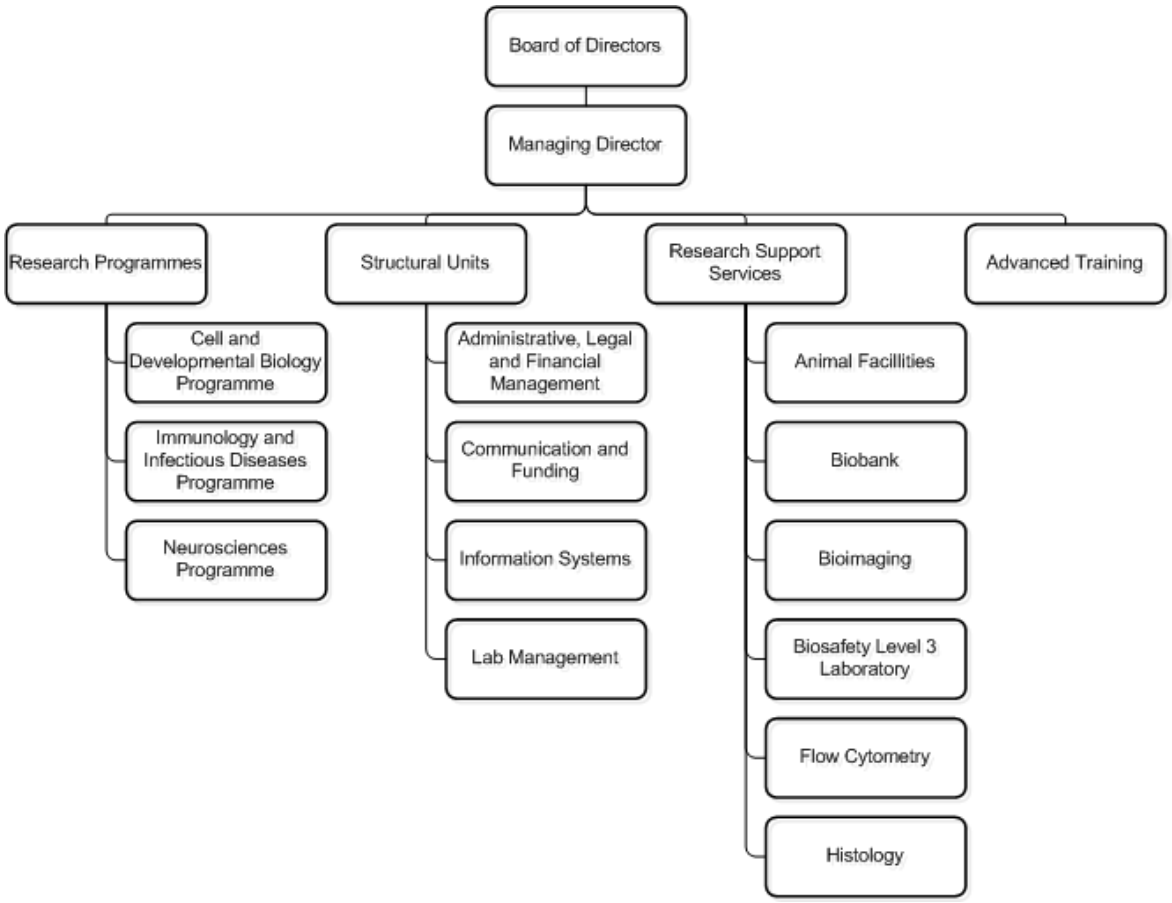


Figure 6: Structure and organization of IMM.

Souce: figure from ref. 1.

The neuroscience research program encloses 4 units:

- Cell and Molecular Neuroscience Unit
- Neurological Clinical Research Unit (NCRU)
- Translational and Clinical Physiology Unit
- Neurosciences Unit

The NCRU is the unit where I had opportunity to do part of my internship. It is headed by Prof. José Ferro and it aims to increase the knowledge, and foster the prevention and treatment of major prevalent and disabling disorders involving the brain (such as stroke, dementia, and Parkinson's disease). The main advantage of the unit is the strong collaboration among the 10 experienced Principal Investigators, based on common clinical research methodologies and particular features of research expertise. Interestingly, in

previous year, the NCRU published 69 full papers in peer-reviewed journals.

This unit also counts with some other qualified human resources: the study site coordinators, a study nurse, and a laboratory technician(3). However, to ensure the proper functioning of the site, many other dedicated are people are required as shows **Erro! A origem da referência não foi encontrada.**.

Figure 7: Operational structure of a clinical research site.
Source: Adapted from figure 1 of ref. 3.

1.2. Laboratory of Clinical Pharmacology and Therapeutics of Faculty of Medicine (LCPT)

Due to the fact that Professor Doutor Joaquim Ferreira exerts activities at different institutions, I had also the opportunity to get some experience at the Regional Pharmacovigilance Unit of Lisbon and Tagus Valley (RPULTV), located in the Laboratory of Clinical Pharmacology and Therapeutics of Faculty of Medicine (LCPT).

LCPT houses 3 functional units: laboratory of pharmacology, Pharmacovigilance unit and Cochrane Review Group.

1.2.1. Laboratory of Pharmacology

The Laboratory of Clinical Pharmacology is responsible for 2 disciplines of the Medicine course in the Lisbon Faculty of Medicine: General Therapeutics and Clinical Pharmacology and Therapeutics. Simultaneously, the unit has been involved in several projects, mostly of them doctoral programs. These generated technical expertise that is essential for the design of clinical trials, particularly related to dose-finding, study of drug interactions and clinical toxicology, bioequivalence studies and establishing dosages.

1.2.2. Cochrane Review Group

The Cochrane Collaboration is an international collaboration network of individuals and institutions that has led the way in setting new standards for preparing systematic reviews. Nowadays, healthcare providers, researchers and policy makers are busy with unmanageable amounts of information which creates a strong need to identify, select and synthesize the highly quality research evidence relevant to a specific topic. This is achieved through systematic reviews.

The Cochrane collaboration is organized in different review groups, composed of persons interested in developing and maintaining systematic reviews. In turn, the groups are coordinated by an editorial team who edit and assemble completed reviews into modules for inclusion in the Cochrane Library.

The purpose of a Cochrane systematic review is to efficiently integrate valid information and provide a basis for a rational decision making (4). It is estimated that it takes about one year to complete a Cochrane systematic review, in which the main steps are: formulating the problem, registering the title in the corresponding Cochrane group interest's area, developing a protocol, locating and selecting studies, quality assessment of studies, collecting data, analyzing and presenting results, interpreting results, improving and updating reviews.

The Cochrane Collaboration has also developed software called “Review Manager” (5). It is a comprehensive tool for developing systematic reviews of therapeutic interventions, including: formatting, reference management, and meta-analysis routines. The use of this statistical method to summarize the results of independent studies can provide more precise estimates of the effects of healthcare than those derived from the individual studies included in a review (6).

1.2.3. Regional Pharmacovigilance Unit of Lisbon and Tagus Valley (RPULTV)

Pharmacovigilance Unit is located in LCPT and is supported by INFARMED and is responsible for processing Adverse Drug Reactions (ADR) reports sent by health professionals (as well as by general public since June 2012) from the Lisbon and Tagus Valley health region (7). The goal is to monitor the safety of commercialized medicines through the promotion and divulgation of safety control methods, especially regarding spontaneous reports of adverse drug reactions.

This unit is also responsible for making periodic reports about new ADR report, planning and executing actions on pharmacovigilance training and outreach activities of the National Pharmacovigilance System (8). The aim of these activities is to alert health professionals to be aware of the importance of reporting, to alert them to the possibility of ADR occurrence and to explain the reports cycle assessment. As part of these responsibilities, the Pharmacovigilance Unit has undertaken several epidemiological studies.

Recently, the unit has registered a meaningful growth in its activity as shows in Figure 8 (9):

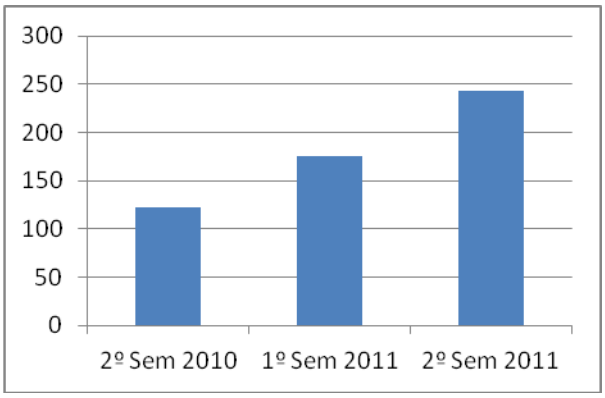


Figure 8: Number of ADR processed in last three semesters.

Source: figure from ref. 9.

1.3. Centro Académico de Medicina de Lisboa (CAML)

Very recently, the Faculty of Medicine of the University of Lisbon, the Santa Maria Hospital (North Lisbon Hospital Centre, EPE) and Institute of Molecular Medicine (IMM), established an institutional collaboration known as Centro Académico de Medicina de Lisboa (CAML).

Its main mission is to promote and support high-quality clinical and translational research. It is expected that the CAML will support the development of the academic dimension and clinical practice qualification, research modernization, encourage medical education and innovation of science health in pre-and post-graduate, as well as streamlining human and material resources, maximizing the synergies resulting from geographic integration and high differentiation of its human resources (10).

It is believed that CAML will become a top-level European Academic Centre in clinical research, with innovative investigator-initiated projects, active collaborations with international networks and partnerships with the industry. It is planned that this centre will add technical and methodological expertise to support study design, conduction and reporting. Furthermore, reciprocal dialogue with IMM's basic and translational units will foster novel approaches to clinical questions, while improving clinical study designs. Synergies with hospital departments can provide access to laboratory and imaging

facilities. Shared training with academic units may present career paths for physician-scientists and other health professionals.

Additionally, a research infrastructure will be available to support clinical and translational research, to promote and facilitate collaborative, multidisciplinary clinical and translational research studies and to educate and train in Good Clinical Practice and clinical research methodology. Its principles include 1) adhering to the highest scientific and regulatory standards, 2) respecting participant safety, 3) ethical guidance in biomedical research and all national and international laws and regulations.

The expertise and infrastructures are aimed to address common barriers that clinical researchers are known to face. These may include: 1) scarcity of dedicated research time, 2) lack of methodological skills and support, and 3) inadequate resources for research in a clinically oriented work environment.

2. State of the art of clinical research

The clinical research unit plays a central role in generating new knowledge in biomedical sciences. One way to turn the scientific discoveries useful to society is through drug development processes. Thus, before a medicinal product obtains market authorisation and reaches the market, it is essential to undergo several investigations designed to evaluate safety and efficacy regarding the establishment of parameters such as toxicity, potency, dose finding and field conditions. To get the marketing authorisation, the pharmaceutical company has to present full information about the therapeutic indications, administration routes and dosages, the expected effects in the target populations, interactions and safety information (including contraindications, safety measures and precautions). This is a long and risky journey.

When a new compound is identified, pharmaceutical companies begin conducting laboratory and animal studies to show the compounds' biological activity in the targeted disease, to identify the characteristics of the investigational medicine and to plan the development. After having some evidences, pharmaceutical companies move forward to the clinical trials that can be classified by phases (regarding time) or types (regarding objective) as shown in Figure 9 (11):

- Phase 1 (Human Pharmacology) aims to study short term safety and tolerability and provide pharmacodinamic and pharmacokinetic information needed to determine a dosage range and administration schedule for initial exploratory therapeutic studies. These studies are carried out in small groups of healthy volunteers given that they have non-therapeutic objectives.
- Phase 2 (Therapeutic Exploratory) involves between 100 and 500 patients to explore therapeutic efficacy through dose escalation designs trials and short term side effects.
- Phase 3 (Therapeutic Confirmatory) trials are conducted in large samples to confirm the therapeutic effect, explore the dose-response relationship and identify some side effects.

Only then, the company applies for the approval. There is also Phase 4 (Therapeutic use) studies which are conducted during and after the approval process with the aim of optimizing the drug's use.

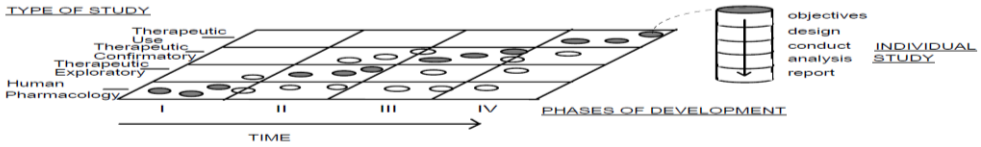


Figure 9: Correlation between Development Phases and Types of Study.

Source: Figure 1 of ref. 11.

Although drug development tries to demonstrate, through controlled studies, a specific generalizable response to a therapeutic measure against a background of individual biological variation (regarding evaluation the quality, efficacy and safety of a compound), the clinical research concept, is broader. It includes:

- The study of the physiological, biochemical and pathological processes as well as the response to specific interventions.
- The study of human health-related behaviour in a wide-range of circumstances.
- The performance of observational interventions aimed to generate records and databases containing biomedical information.

As a complex and multidisciplinary area, it requires input from different professionals with numerous backgrounds in order to be successful (12).

Figure 10 shows the position of each element of a clinical research centre.

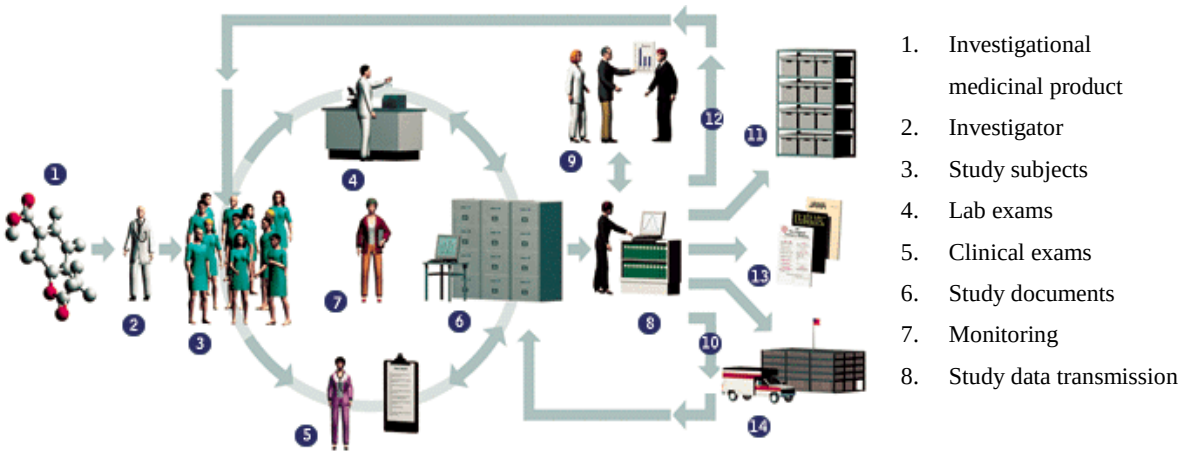


Figure 10: Interface of clinical services in the clinical research.

Source: Adapted of ref. 12.

These requirements are legislated. Actually, this is a highly regulated area. There are several national and international bodies releasing guidance documents related to clinical research:

- *International Conference on Harmonization* (ICH)

  International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a joint initiative between regulatory authorities and the pharmaceutical industry from Europe, United States and Japan to discuss scientific and technical aspects of drug registration.

  ICH´s mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner (13).

- *International Standards Organization* (ISO)

  ISO is an independent, non-governmental organization made up of members from the national standards bodies of 164 countries. It was created 'to facilitate the international coordination and unification of industrial standards' (14).

- *Council for International Organizations of Medical Sciences* (CIOMS)

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949 with the purpose of serving both the scientific interests of the international biomedical community in general, facilitating and promoting international activities in the field of biomedical sciences and maintaining collaborative relations with the United Nations and its specialized agencies (15).

- *European Medicines Agency* (EMA)

  EMA is the regulatory agency of the European Union with the main responsibility of protecting and promoting public and animal health, through the evaluation and supervision of medicines for human and veterinary use. It is also responsible for the scientific evaluation of applications for European Union (EU) marketing authorisations, acting in referral or arbitration procedures where there are concerns over the safety or benefit-risk balance of medicines approved or under consideration by Member States in non-centralised authorisation procedures, monitoring the safety of medicines through a pharmacovigilance network and stimulating the innovation and research in pharmaceutical sector (16).

- *United States Food and Drug Administration* (FDA)

  Food and Drug Administration is the United States of America's agency responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, pharmaceutical products (17).

- *Portuguese Authority of Medicines and Health* (INFARMED)

  INFARMED is a Government agency accountable to the Health Ministry. Its purpose is to monitor, assess and regulate all activities relating to human medicines and health products for the protection of Public Health (18).

- *Portuguese Ethics Committee for Clinical Research* (CEIC)

  The CEIC is responsible for monitoring Health Ethics Committees, receiving all applications for ethical review and is accountable to the Minister of Health. It acts

as a consultative body alongside the Council of Ministers (19).

During my internship, I had the opportunity to work with some guidance documents released from these institutions:

- ✓ "Clinical Trials Law" is a transposition of Directive 2001/20/CE from April 4th into Decree-law 46/2004 of August 19th.
- ✓ "Good Clinical Practice Law" from the Directive 2005/28/CE of April 8th transposed to the Decree-Law 102/2007 of April 2nd.
- ✓ "Medicinal products for Human Use" is the European Directives 2001/83/EC which has been transposed to the Decree-Law 176/2006 of August 30th. In December 2010, the European Community released a new directive 2010/84/EU and a Regulation Nº 1235/2012 which became effective in July 2012.
- ✓ "The individual's personal data protection law" is the Law nº67/98 which results from the transposition of the Directive 95/46/CE October 24th.

In this demanding environment, the concept of the physician-scientist as "a broad-based investigator who discovers fundamental biological mechanisms and applies these insights directly to the cure of disease" is facing several challenges (20). In addition, the scientific community's eyes are fixed on investigators achievements. Although the basic research is flourishing as never before and the number of new entities patented is still rising, the number of new drugs which achieve the market do not keep up, especially when compared with the growing investment as shown in Figure 11. This has alerted for the need of developing new methodologies able to improve the success rates of drug development, which can only be possible with the interest and commitment of clinical investigators (21).

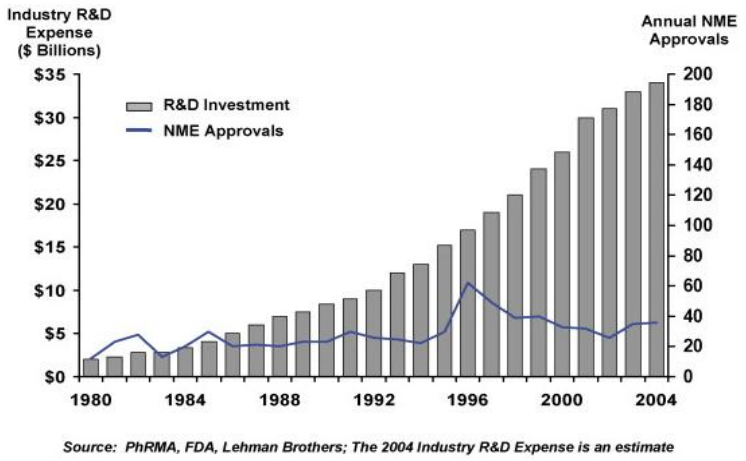


Figure 11: Annual research and development expenses for the pharmaceutical industry and productivity measured as the number of new molecular entities (NME) during the period 1980–2004.

Source: figure 1 of ref. 21.

The need for developing sustainable science with high productivity has promoted the development of science management facilities with the aim of supporting the physician-scientists in a wide range of roles, namely:

- Identification of national and international funding opportunities
- Systematization and dissemination of funding programs
- Promotion of strategic scientific partnerships
- Support in the preparation and submission of applications, particularly in administrative and financial issues;
- Assistance in the negotiation of contracts;

The recognition of the benefits of piecing together the capabilities/skills of a wide range of professionals brings forward the importance of knowing how to collaborate with each one of them. To help our team to achieve its goals, we really have to know each other roles, expectations, capacities and what we have in common. Only in this way can we complement each other's job with a direct impact on team productivity and output value.

3. On the job training

In this section I describe the activities developed during this 10-month internship: in the beginning in a clinical research unit as a study coordinator and co-monitor of an observational study, and in the last months at a Pharmacovigilance unit. In conjunction with these activities, I was also involved in a wide range of science management activities.

3.1. Clinical Research Unit

3.1.1. Study Coordinator

On my first days at the clinical research centre I had the opportunity to get familiar with the site routine, the protocols of the on-going studies and the team. I was also introduced to NCRU history. Since the unit creation until the moment I left, more than one hundred studies had been conducted in several diseases as shows Figure 12.

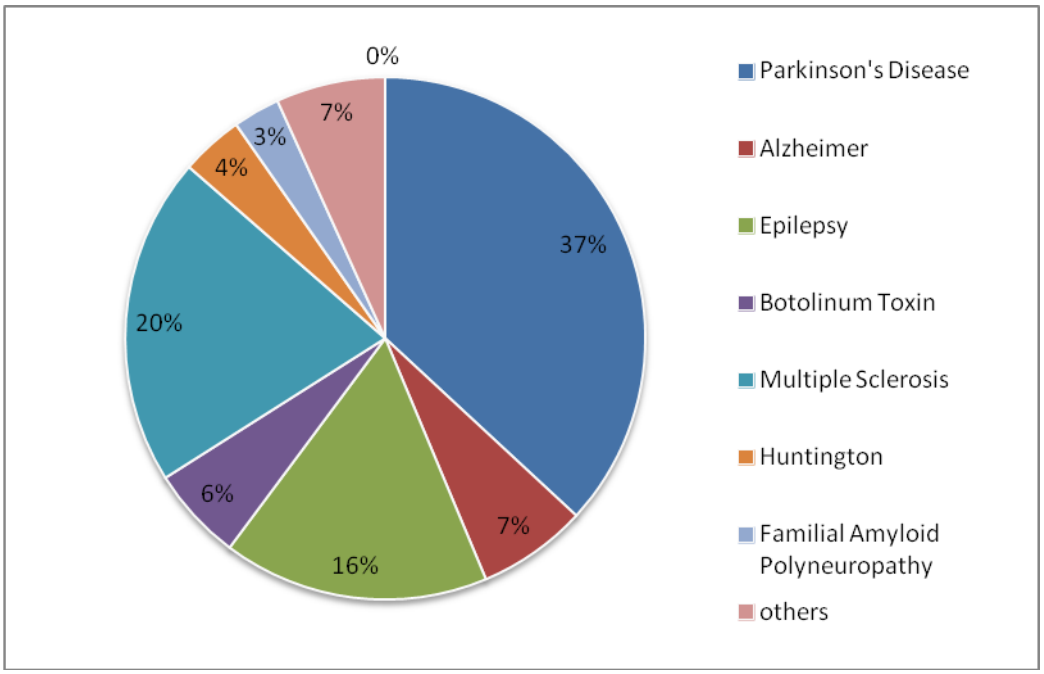


Figure 12: Diseases addressed by both clinical trials and observational studies.

Regarding the clinical trials, the site has experience/expertise in the 4 phases of drug development. As illustrated in Figure 13 the most performed are phase 3 trials.

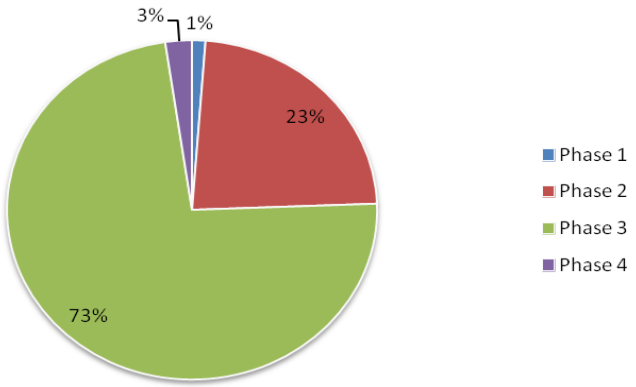


Figure 13: Proportion of clinical trials phases performed in NCRU.

This period allowed me to be able to, initially follow what was being done, and secondly, to become a meaningful support to the team. It was especially important to realize how NCRU was organized and to know the people I would work with.

Knowing the team and the roles of each element, it was possible to understand the routine work done, the timing of each task and the role and value of everyone:

Principal investigator (PI)

PI is the maximum responsible for the conduction of the trial at all levels. He is responsible for following the protocol procedures and conducting study visits, He ensures if the research team has the education and technical skills adequate for the tasks required per protocol, if each element has received the required training and if the equipment and facilities needed are available for the trial.

He is also responsible for attracting and bringing new clinical trials to the centre.

Study coordinators

Besides the old-fashion definition of "protocol implementation" (22), study coordinators are responsible for all logistic management, from scheduling of patients´ visits, according to protocol windows, including support the investigators, and prepare monitoring visits preparation and finally to assist monitors. They are also responsible for organising the study procedures according to the protocol for each visit and patient, guiding subjects and answering the minor doubts. Usually, study coordinators also measure vital signs, perform electrocardiograms (ECG's), process biological samples and pack them in the right

conditions to be sent to the central laboratory. In short, SC plays a pivotal role by connecting the patients, investigators and sponsors representatives.

Investigators

Investigators are responsible for the recruitment of the subjects by asking them to take part in clinical trials, explaining the study objectives and procedures, the benefits for the patients and relatives and when the subject agrees to participate, the investigator is also responsible for obtaining the Informed Consent Form (ICF). They are also responsible for determining subject eligibility to be included in the trial by analysing the inclusive and exclusive criteria. While subjects are participating in the trials and in the follow-up period, the investigators are responsible for performing the medical assessments, the key trial measurements and ensuring the well-being of patients, including withdraw patients when and if they decide to. Regarding the study medication, investigators are responsible for prescribing it as well as administering it or giving useful recommendations. They are also asked to collect the subject information required per protocol, to make Case Report Form (CRF) entries and corrections, resolve queries listed in the Data Clarification Forms (DCF) and sign the CRF. Regarding the subjects wellbeing, it is the investigator's responsibility to treat and report any Adverse Event to the sponsor, particularly serious/life threatening unanticipated events.

Pharmacists

The pharmacists are responsible for receiving, handling and storing the product according to the manufacturing specifications and the study protocol. Pharmacists are also responsible for dispensing and accounting the investigational products. In our specific cases, the prescription completed with the information obtained from the Interactive Voice Response System (IVRS) can be sent to the pharmacy by email and a pharmacy assistant brings the Investigational Medicinal Product (IMP) to the site. Then the investigator checks the batch number and when it matches with the number obtained in the IVRS, the IMP is delivered to the patient.

Laboratory technician / study nurse

The laboratory technician and the study nurse are responsible for the collection of biological samples according to the protocol procedures.

As a SC, I had the opportunity to follow the whole cycle of activities involved when performing a Clinical Trial:

1. Feasibility contact

Before a site is selected to participate in a clinical trial, the sponsor ensures the site is qualified enough to conduct the study based on the clinical protocol. The best way to assess a site's qualification is by using a feasibility questionnaire. This document consists of a series of modules designed to measure the site's experience and familiarity with clinical trials. The aim is to help the interested sponsor to choose the sites and investigators according to the experience and facilities in order to avoid compromising the final results. Usually, this questionnaire is filled in by the principal investigator.

Sponsors look for the investigators with the particular and necessary medical expertise, sufficient resources and trained staff to conduct the trial.

It is also common for the sponsor or Contract Research Organization (CRO) to schedule a feasibility visit to ensure facilities present the adequate characteristics for the successful performance of the study according to the Good Clinical Practice (GCP) requirements. In case of any required equipment not being available, the sponsor provides it.
At the end, the Principal Investigator (PI) is invited to sign the confidentiality agreement. After that, the study protocol is presented and a chance is given to the PI to make any comment or ask about any issues which were not clearly exhibited. In addition, the PI usually outlines the main difficulties he/she forecasts hoping to listen to any helpful suggestion or even, a protocol amendment.

Then, the number of expected patients to be included is agreed upon and the financial protocol discussed. At this time, the submission to the Administration Board (AB) and Ethics Committee for Health of CHLN (EC) begins. This includes several documents:

- A request from the PI to review the CT protocol
- A Statement from the Head of Neurology Department

- EC questionnaire completed
- CT dossier to be submitted to EC
- A financial contract
- Investigation team dated and signed CV's

The financial contracts are delivered to the Neurosciences Department to be approved by the AB; the remaining documents are sent to EC which will ensure the study is appropriately designed to meet its stated objectives taking also into consideration the local law and regulations.

Once the approval is announced, the results are communicated to the Sponsor/CRO.

2. Investigator's meeting

The purpose of these meetings is to train and motivate teams to meet the challenging demands of the protocol as well as to recruit the large numbers of patients that are essential to its success. It is very common to have the whole team involved in the clinical trial together on these meetings: investigators, SC, clinical and medical monitors and quality assurance and senior managements. The most important investigator meetings happen before the trial begins although other meetings could be planned during the ongoing study.

3. Site initiation visit (SIV)

The objectives of SIV are to review the adequacy of the site, the training and experience of the study staff, the access to the right patient population, and the site's interest in the study. If the site is not motivated or if there is already an ongoing study that would compete for the patient pool, the site is seen as a not so good recruiter.

Typically, the clinical monitor thanks the site for hosting the trial and informs why they have been chosen to participate in the study. During this visit, the monitor requests a tour of the facility to visit the labs, pharmacies, and other areas where the research will be conducted to ensure they are adequate. For example, both labs and pharmacies should have restricted access and the site should know where it will store the IP and this location should be locked. If blood or tissue samples will be stored at the site, the monitor checks freezers

and ensure that they maintain adequate temperature logs and have standardized sample handling protocols and training. Usually, the monitor confirms the supplies reception.

During this visit, both an investigator and a study coordinator must be available. Time to discuss the basic fundamentals of the protocol and how that relates to the feasibility of recruiting potential participants is also requested so a significant time is spent reviewing the study protocol design and identifying problems and concerns.

The PI is also requested to be available for specific parts of this meeting to discuss the Investigator's Responsibilities. Usually the investigator delegates some of the responsibilities to others (i.e. sub-investigators, study coordinators…) but ultimately, he is responsible for all actions and for conducting the study. To ensure everybody knows his/her roles and responsibilities, it is written in the delegation log which is kept in the investigator site file. Regarding regulatory obligations of each member of the team, some training activities are also scheduled.

In short, the topics discussed include are:

- ✓ Clinical Trial Protocol
- ✓ Informed Consent Form
- ✓ Investigator Brochure
- ✓ Investigator Site File
- ✓ Investigational Product
- ✓ Case Report Form
- ✓ Source Documents
- ✓ Adverse events and serious adverse events report and procedures
- ✓ Central Laboratory
- ✓ Monitoring requirements

Clinical monitor reviews with the team CRF the completion instructions and the requirements for records management/retention. I observed that monitors usually remind

PI that a timely access to subject's records and an acceptable time frame for completing patient data CRFs will be required.

They are also available to answer queries regarding the protocol and logistics procedures. Special attention is given to drug handling requirements, enrollment, consent procedures and adverse event reporting procedures. At the end of the visit, if there are unresolved questions, there is a commitment to include resolution for those in initiation visit report.

Sometimes, the Clinical Monitor (CM) is accompanied by a Project Leader, Medical Monitor, or even a Data Manager depending on the desire of the sponsor.

In this visit, it is common for the CM to organize the study cabinet: archiving study documents, fills in delegation signature log, visit log, activates IVRS/IWRS and checks the correct functioning of ECG or other equipments.

At this moment, the site recruitment period is opened.

4. Patient visits

When a patient is identified as a possible candidate for a clinical trial, usually in the outpatient clinic of Neurology in HSM, the investigator introduces the trial to the patient and delivers a copy of the ICF to the subject giving the patient the opportunity to decide with his/her family to enter or not in the trial. After this first approach, another visit is scheduled, or phones call, to know if the patient is interested to take part in the study.

Usually, I prepared the patients visits the day before. This allowed us to know the procedures of the visit and to avoid losing time looking for the required material on the day.

Sometimes, and according to protocol, a phone call was performed to remind the patient and/or caregiver of the time of the visit and to discuss any other aspect.

For some clinical trials, I had the opportunity to create worksheets for each visit with the procedures required in the protocol to guide the investigators and to avoid that any tasks would be forgotten or performed in the wrong order of the sequence specified in the protocol. Usually, these worksheets also worked as a source document.

5. Periodic monitoring visits

The objective of these visits is to make sure the study is conducted, recorded and reported in accordance with protocol, GCP and SOP's requirements without compromising patients' safety and data accuracy.

A monitoring plan is developed by the sponsor and/or CRO which includes the frequency and duration of periodic monitor visits. The purpose of these visits is to evaluate the way the study is being conducted and to perform source document verification. These visits can occur every few weeks or once a year and can take less than one day or up to several days at a time.

Usually, the clinical monitor sends an email describing the visit´s goals. This allows the study documents being organized to be reviewed.

I also had the opportunity to see how monitors organized their jobs. Our research site had a workspace separated from the research study team with internet access where clinical monitors performed the source document verification and listed the queries founded. A specific time is scheduled for the study coordinator and/or investigator to meet with the monitor towards the end of the visit to share findings, identify needed corrections and answer questions. At the end, a list of unsolved queries was left at the site or sent by email.

The most common objectives of periodic monitoring visits were:

- To ensure CRFs were completed according to subject status.
- To confirm Serious Adverse Event (SAE) forms have been submitted and are available for review
- To confer whether CRFs are completed according to source documents

- To confirm informed consent forms are dated and signed for all the enrolled participants.
- To check whether the investigational product is correctly dispensed and returned and if it matches with the drug accountability record forms.
- To assess subjects compliance.

6. Close-out visits

A close-out visit is planned when the research study has been completed at a site. This type of visit can take the form of an on-site visit or, in some cases, be conducted via a telephone call. Some close-out visits are also combined with a final periodic monitoring visit.

Tasks performed during the close-out visit include:

- The discussion of timelines and strategies for the completion of outstanding case report forms and queries
- Returning or destruction of study drug
- Collection of outstanding patient data forms and study forms such as the screening and monitoring logs
- Performance of a final review of the study file documents
- Discussion of plans for record retention
- Discussion of ongoing investigator responsibilities

During my experience as a study coordinator, I received different instructions for different moments:

- Before the patient visit:

The SC trained me to find in the protocol which requirements where necessary for the patient´s visit. According to the planned aspects required, we put together the materials (patient folder, scales, vital signs sheet, samples kit, investigational product dispensing

form, study protocol and flowchart to avoid protocol deviations, if applicable) and identified the material to ensure the material was not used with another subject.

- During the patient visit:

According to the protocol, I performed the vital signs measurement (temperature, blood pressure, pulse), I helped the lab technician or nurse collect the samples by handling the pieces of laboratory kit, centrifuging them when necessary and packing them to ship according to the laboratory manual of each trial. I also performed ECG, asking patients to keep calm and in the right position and putting the electrodes in the right places and record the ECG in the machine. When the pharmacist assistant delivered the investigational product, I received instructions how to check the kit dispensed.

- After the patient visit:

The SC taught me about data entry tasks and handling CRF and eCRF's, shipping the samples collected to the central labs, solving queries and sending the ECG records for a central assessment.

In every stage of the studies, it was possible to see the whole team´s commitment in ensuring the wellbeing of study subjects. Since the beginning, investigators encouraged subjects to contact the site whether they experience any untoward event. During each visit, investigators asked about adverse events (AE's) which might have occurred since the previous visit by active interrogation and reviewing the results of clinical measurements and laboratory investigations. When an adverse event is detected, the seriousness is assessed and AE or SAE forms are fulfilled according. It is a time demanding task but later I understood why so many details are required.

3.1.2. Clinical Monitor

In parallel to the activities as a study coordinator, I had the opportunity to be a co-monitor of a prospective observational study of the European Huntington's Disease Network, called "Registry". This is a multi-centre, multi-national observational study. The main goal is to map the Huntington Disease in order to increase the knowledge about the disease to find new and better treatments for it (23).

The site monitoring is performed to ensure the high quality trial conduction. Usually, the extent and nature of monitoring visits are based on the objective, purpose, design, complexity, size, endpoints of the trial and risks involved.

The “on site” monitoring visits are used to review individual case histories, to verify the adherence to protocol and GCP principles, to ensure the ongoing and the appropriate data entry and to guarantee quality control procedures

The clinical monitor also ensures the data is completed, reliable and processed correctly.

As a co-monitor, I learnt how to prepare each site visit by combining the date and time to ensure the availability of the study team and sending an email informing the time of arrival and the visit objectives with a description of the documents and subject pseudonyms which will be verified in order to allow the study team to prepare the visit.

During each visit, I had the opportunity to:

- Review the ISF and list the missing documents or information to be asked to the site team
- Check whether ICF’s were correctly dated and signed
- Solve queries with site team
- Confirm the patient identification log
- Verify the source documents
- Review the e-CRF
- Help study team with logistical difficulties.

After the visit, a follow-up letter is sent describing what has been done during the monitoring visit, thanking the team support and praising the commitment shown.

I also co-wrote a monitoring visit report that included:

- number of participants recruited
- number of participants monitored
- pending queries to be solved

- ICF incomplete and missing
- protocol deviations
- adherence to study visit scheduled
- correction of previous issues

Then, the monitoring visit report was sent to the international coordinator team and the follow-up email to the site visited.

Unfortunately, I did not have the opportunity to apply the procedures to open a new site or prepare a SIV. However, understanding the way routine tasks are performed, in addition to what "monitoring guidelines" describe, was very important and useful.

Furthermore, the HSM was the Portuguese language coordinator which brought me the possibility to translate some documents entitled "article of the month" and get an idea of the achievements this project has made possible.

3.2. Science Management

High-quality clinical research is essential to understand diseases and improve health care. Each research proposal should provide the potential to add to the existing body of knowledge, to advance understanding, and to help alleviate human disease and suffering. However, converting the proposal into reality requires grant funding (24). In an era of reductions in research budgets and application success rates, the ability to construct a well presented, clear, articulate proposal is becoming more and more important. Obtaining research funding is a key element to the research process (25). Thus, the competition for funds to conduct clinical research is intense, and only a minority of grant proposals actually receives funding. Given this environment, understanding the essentials of grant writing is of fundamental importance to the academic clinical researcher—for career development and for advancement of clinical research projects and programs (24).

Therefore, the main objective of Science Management is to provide project management, prioritizing tasks and to establish timelines according to the site investigators interests while assisting clinical researchers writing applications for external grants proposals, editing manuscripts, developing budgets and producing other scientific documents and projects (26). In other words, science managers have a central position in clinical research projects.

Hence, a science manager usually performs scientific writing tasks which support researchers in their applications for grants and manuscript submission to scientific journals, ensuring the compliance with all relevant guidance and regulations in order to improve the quality and impact of these documents in a transparent and rigorous manner. The aim is to facilitate access to national and international grants in the clinical research field, taking advantage of the opportunities for interdisciplinary applications and international networking collaborations.

During my training, I had the opportunity to do some of these activities related to science manager.

3.2.1. Look for grants opportunities

Initially, I looked for research opportunities through grants and prizes. Organizing the grants chronologically, we could easily have an idea of the grants deadlines. Having this information updated, it is possible to choose the most appropriate opportunities according to our interests and available time. Obviously, a continuous update is required because calls are opening all the time.

During this task, I found most funding opportunities were competitive calls, which we called "grants". There were several types of grants according to specific funding schemes:

- large grants for collaborative research
- research grants
- travel grants
- small grants
- prize awards
- fellowships

Factors that determine the type of funding pursued included 1) the activity pursued by the investigator, 2) the research subject area, 3) the geographic area, 4) the investigator's career level, 5) the investigator's affiliation with a professional society, 6) the size of the grant and 7) the source of funds (27). Regarding the national grant scenario, funding may come from 3 sources:

- Government (e.g. FCT, QREN…)
- Charities and Foundations (e.g. Champalimaud Foundation, …)
- Corporations (e.g. Bial, Pfizer,…)

Apart from public, private and foundations sources, there are also international organizations which constitute a good chance to apply. For instance, the 7th Framework Program is one of the most known initiatives because it presents opportunities in several research areas.

One of the most interesting things I have learnt was that usually there are more than one source of money for any given project idea and most funding agencies have multiple

funding programmes. But, although there are many funding opportunities, there are also many conditions that limit eligibility. So, the idea is to search a lot and get as many help as possible. Identify the common pitfalls in research applications before submission can lead to a stronger application (28). Application of specific recommendations, already published to help grant writers, improves the quality of areas commonly cited as deficient and will make the task more manageable for anyone who writes grants proposals.

3.2.2. Scientific papers writing

While I was looking for funding opportunities, I was involved in the rearrangement of 3 scientific articles for publication:

- "Espresso coffee" for the treatment of excessive daytime sleepiness in Parkinson's disease: results of four n-of-one clinical trials
- Usefulness of the OSLER Test to screen for risk of sleep attacks in PD patients
- Effect of antiparkinsonian drugs on sleep disorders in Parkinson's disease: data from adverse events in clinical trials

They were related to studies performed before I came to the unit. However, I tried to write them following a usual method as shows Figure 14:

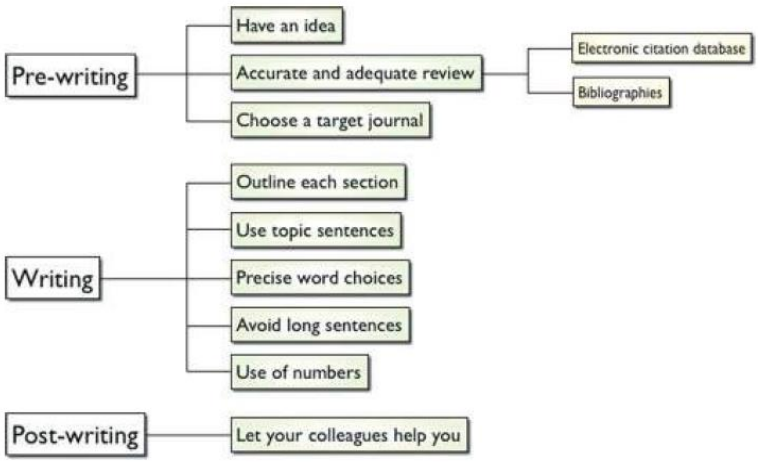


Figure 14: Steps to write a scientific paper.

Source: figure 1 of ref. 29.

This was a process which took a few months.

To begin, I had to conduct a literature review to find the strengths and weaknesses of our study and to find out whether something similar had been done meanwhile and, at the same time, new critics which have appeared in those articles used as references (29).

After, I had to find journals which could be interested in publishing these specific articles. This step is important to determine our potential readers and identify their needs. Furthermore, each scientific journal has its own publication rules, so we have to consider the article structure required to avoid rejection for this reason (30).

This choice was made based on the citations number and the impact factor. The idea was to submit first to the most promising journal and if the publication request is denied, choose the following one. I edited the articles according to the journal rules.

Then, I began organizing the information according to IMRAD structure: Introduction (why are we writing?), Methods (what did you do?), Results (what did you find?) and Discussion (what does it mean?) (31). According to the purpose of each heading, I selected specific information (32):

1. Title

Although the title has to be short, it has to capture the target public attention by giving the general idea of the paper content. Basically, it has to become a "looker into a reader" as J. W. Howie said (31).
Looking for many other papers already published, I found the key information is the subjects' identity, the specific aspects addressed and the variables manipulated.

2. Authors

Here, I perceived how difficult it may be to decide the order in which each author appears. In one of the articles, it was necessary to mention 2 authors as having the same commitment.

3. Abstract

Written at the end, usually in 4 topics structure: background, methods, results and conclusion.

4. Introduction

In this section I learned to include the description of the problem being studied, the specific research questions and some articles related to the problem without doing an extent literature review. The goal is to show the pertinence of this publication highlighting the current theories, the knowledge gap and conflicting data.

5. Materials and methods

In this section, I recognized the importance of describing enough details enabling the reader to interpret and replicate our study. This includes giving information about the protocol: inclusion and exclusion criteria, research design (the plan chosen to answer the research question), the outcomes of the study, how they were measured and the analysis procedures.

I have also noticed that methods of elimination of errors, ethical and statistical considerations should be mentioned distinctly.

6. Results

One of the most important issues in this section is to present data in a logical order and focus on the question or hypothesis put forward, emphasizing the important observations but never including our opinions.

I have identified some common things which should be avoided such as overstating the results (figure clearly shows…). On the other hand, I learnt data should always have statistics: statistical significance and the statistical test used to evaluate the significance.

7. Discussion

The purpose of this section is to explain the meaning of the results to the readers. Here I learnt to include information such as the major findings and whether the proposed

hypothesis are supported or rejected, the discrepancies between findings and previous reports, the study's strengths and limitations, the importance of findings.

Finally, we wrote a short summary or conclusion about the importance of the study and offering recommendations for further research.

8. References

Regarding the references, I have learnt they should not be an infinitive list or, on the other hand, only a few numbers. It should be a reasonable proportion, so only the most important ones are used. The content of the paper will show whether the references quoted were carefully read and well understood.

To edit them according to the journal requirements, the easiest way I found was to use EndNote®, reference management software.

Obviously, all of this work was performed based on the inputs from all authors. So, only when everyone agrees with what is written, the paper is submitted.

3.2.3. Application for FCT call

Another opportunity I had during my internship was to coordinate an application for an FCT call.

In January, I began preparing the submission process by reading the guidance launched by FCT in order to know how to plan the work. The following step was to join the team organized by Professor Joaquim Ferreira and to explain the scope of the project in more details. In order to gather as many people as possible, all team members were asked to express their preference between two dates for the meeting.This meeting occurred on January 24th.

As expected, not everyone was available. So, I sent a summary of the meeting with the presentation so that everyone could get along with the decisions taken.

In this meeting, members were invited to join as small working groups according to their area of expertise and think about what they were willing to do to contribute to the project. In addition, some administrative information was also asked. For instance FCT requires the investigators' CV's updated and a personal code which has to be included in the application given by each investigator in order to ensure their desire to be part of the team.

Working with such an experienced team showed to be a great advantage. Something very useful that I learned was that we should conduct all our efforts throughout the submission process keeping in mind the ultimate goal we want to achieve.

The submission step to a research grant must always be borne in mind. It includes 4 major steps as shows Figure 15: reflect, plan, write the grant and rewrite and submission.

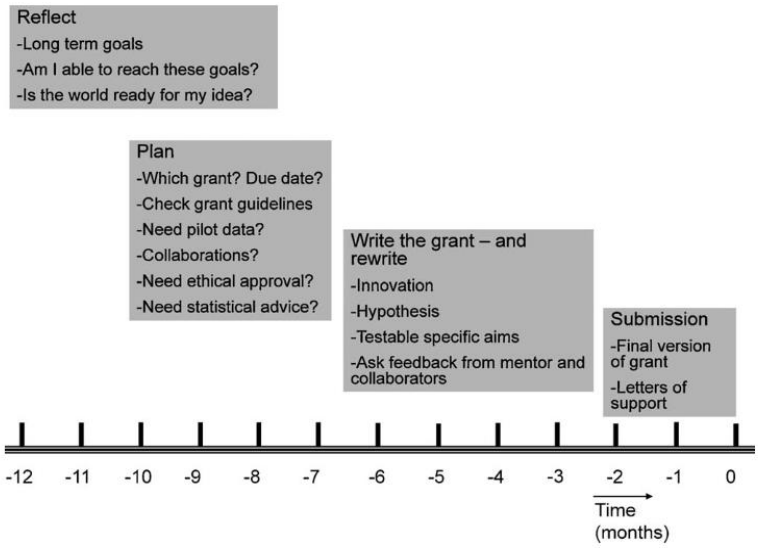


Figure 15: Timeline for preparing a grant application.

Source: Figure 1 of ref. 25.

The application submission only includes the stage of search for a scientifically interesting idea and writing it to submit. But, as the picture above shows, since the beginning we are thinking about the submission deadline.

This way of thinking makes it easier to write the proposal. An important thing to keep in mind was keeping our thoughts organized, even if only in our heads. To do that, I tried to find answers to the following issues:

1. Purpose/aim
2. Objectives and goals
3. Constrains (limitations and needs)
4. Assumptions
5. Audience
6. Defining who does what and when

One of the most important challenges I faced was managing the time to complete our tasks. So, I learnt it was important to a) set goals (plan) which involves keeping thorough records; set short, medium and long term goals and take time to think; b) set priorities (to do lists) classifying tasks according to its importance and urgency and c) use small units of time.

While I was involved in the coordination of this submission procedure, I observed that approaching a funding proposal is an opportunity to fund an idea we are interested in and, at the same time, it is an opportunity for the funding agency to meet its goals, so we had to find a balance to please both. Thus, when we find a grant opportunity that we think may be interesting and suitable for our goals, we have to check carefully what the funders want to fund and consider the criteria used by funding agencies in its evaluation (such as: expertise of the applicant, the research question, knowledge of the field, soundness of the research design, relevance, ethics and budget). Addressing these criteria will assist the applicant in developing an effective grant proposal (33).

Writing is by far the most time consuming part: we need time to let others read the proposal, time for waiting for other people's work, time to refine your style, and time to include writing in normal work duties.

In order to motivate our team and ensure everyone is on track, 2 team meetings were performed:

- January 26th

This meeting enabled people to know who is going to be part of the project as well as to discuss the main objective of the project. Partners were then invited to think about tasks they could perform to enrich the final achievements and send to be coordinated centrally.

- February 22nd

At this time, the proposals were shared and the path to follow was traced. The period of one week was given for all working groups to send a final input for the project.

After that time, all the gathered information was combined and final version of the application was developed.

During the proposal writing, I noticed 3 issues of special concern:

- Team

The researcher and his team should be well qualified to carry out the project. This capacity as a performer is assessed through the quality of prior work, publications, and team's CV's, the complementarities of roles and skills and the time dispensed to the project by each member. Another point which is considered is whether the extent of the achievements are demonstrative of scientific thinking/creativity.

- Project

The proposed research should address important challenges and it should have suitable ambitious objectives. The potential achievements should also open new and important, scientific or technological horizons. On the other hand, attention is also given to whether the scientific approach is feasible, comprehensive, and appropriate and could be achieved within the proposed timescales and resources. Ultimately, it is evaluated whether the possibility of a major breakthrough justifies the risk involved.

- Host

The description of the host institution has to ensure the availability of adequate facilities to carry out the research as well as an appropriate intellectual environment to assist the project and research team.

These features are shown throughout the whole application.

Our project included the preparation of the following components:

- Title

In few words, we tried to say what the project was about and to stimulate the evaluators' curiosity. The goal was to make them believe this project would bring useful conclusions and be interesting for others.

- Summary

It summarizes the main argumentation leading to the proposed idea for research. Done at the end, it became significantly easier. I observed this is a very useful part to establish empathy with reviewers.

- Introduction, team background and state of the art

In these sections, we described our institution, the team achievements and the previous work related to our project. The goal was to justify the timing, innovation and impact of the proposal to convince evaluators that the team has the adequate background on the proposed field, thus the project emerges as realistic, relevant and at the right time. This will give confidence to the evaluators to fund the idea.

- Specific objectives

The aim in this section is to show the evaluators that our objectives match with the interests of the evaluators. It is important transmit that it is feasible, relevant, specific and quantifiable.

- Plan and methods, specific tasks and outcomes (deliverables, milestones)

In this section, the tasks are described and how the expected results will fulfill the objectives are explained. A temporal link between tasks and whether they are dependent or independent from each others is established. The resources needed for the task is referred here, as well as the role of each member in the task.

One important lesson I learnt is to identify risks per task or for the whole project and present a contingency plan (plan B).

- Existing resources and budget

In this section, I described the equipment and models available at the Hospital and IMM which could be used for the project. On the other hand, the equipment which did not exist was included in the budget to be bought.

To calculate the budget, technical consumables, investigators' fees, administrative costs and adaptation of facilities were also included. At the end, I also included a percentage for overheads. These calculations are based on institution and legal rules.

One useful point I had understood was the importance of keeping a copy of our original calculations and justifications in order to be easier to make future adjustments.

- Timelines

The timelines are requested on the form of flowcharts. It gives a visual aid to understand what procedures are dependent on each other and which ones could be performed concomitantly.

In summary, I discovered that writing a grant proposal requires significant preparation and groundwork. To be a successful grant writer, we need to have a strong interest in the research topic at hand. At the same time, we need to have a clear understanding of the sponsor's perspective and interests (27).

Furthermore, writing a grant proposal forces us to create, define, and refine the research project continuously. In fact, the time spent to fully conceptualize and synthesize the proposal is not a waste. It will enhance our ability to conduct a successful study and will provide the framework for future reports of the work (24).

3.3. Pharmacovigilance

Nowadays, when medical products are introduced in the market or into public health programs, they only have been tested on a limited number of carefully selected individuals: those with clear-cut evidence of the disease in question, who are not taking other products and who do not have other conditions that might interfere with an analysis of efficacy of the product being tested. Furthermore, drugs are tested for a short period of time and then, they reach the market and they are used in a much wider group of people and usually for longer periods. So, when new drugs are approved, what we know about them regarding safety is very limited. Although the sponsor may already know some adverse drug reactions (ADR), even reported them to the responsible authorities, we do not know all of them, especially the rarest ones. Thus, the post marketing surveillance becomes important to discovery new ADR previously unidentified.

ADR are defined as "a response to a medicinal product which is noxious and unintended" (34).

Within the purpose of collect and treating data related to ADR, the Pharmacovigilance System has been established.

RPULTV, as one of the regional units of the Pharmacovigilance system, has Standard Operation Procedures already implemented, so the daily routine is written and I was given access to it to consult every time I had doubts. Initially, I followed and did all the tasks performed with the person who used to do them. Gradually, I began doing each of the RPULVT tasks by myself.

To begin, I was introduced to the team who ensures the routine activities:

* The head of RPULVT who directs epidemiological projects, trainees in the unit, human resources and represents the unit.

* The clinical coordinator, expert in clinical pharmacology who is responsible for the clinical assessment of the cases reported, to compare to what is already described in

the Summary of Product Characteristics (SPC), to decide about emit analyses reports about potential alert signs and outline additional information required for a complete assessment of the reported cases.

* Pharmaceutical coordinator, responsible for checking the data introduced on a national database named Medicinal Products for Human Use Vigilance System (Sistema de Vigilância de Medicamentos de Uso Humano) "SVIG" , to write and send analyses reports about alert signs, plans and formative actions related to Pharmacovigilance and advertisement of the Pharmacovigilance National system.

* An administrative assistant who is responsible for reception and report validation, data entry in SVIG, answering report forms and managing administrative material and mail box.

Erro! A origem da referência não foi encontrada. shows how RPULVT is organized (35):

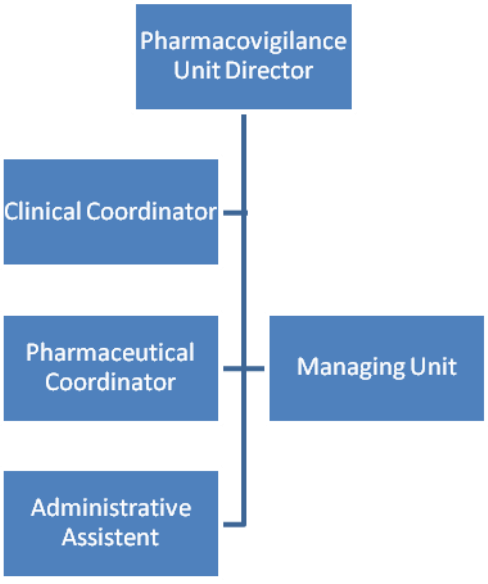


Figure 16: Organizational structure of RPULVT.
Source: figure reproduced from ref. 35.

3.3.1. Report procedures

When reports are received either by phone, fax, mail or email, they have to be validated. This means there is a criteria they have to fulfil in order to be assessed in the RPULVT:

- It should be sent from the operation area of the unit. Otherwise it will be sent to the unit responsible after minimum criterion has been checked.
- The suspected drug should be actually a drug.
- The report should contain at least 4 fields filled in which contain:
  - A health professional
  - A patient
  - An active substance (cosmetics and dietary supplements are not included)
  - At least one sign of an adverse drug reaction.

Once these criteria are fulfilled, the report is dated and signed and an identification code is assigned to it. Whenever some kind of information is missing to validate the report, it can be obtained by contacting the reporter.

When the report is not received through a standard report sheet, data is used to complete one.

After, report data is entered in SVIG and the original report is scanned and attached to it. The SPC of the suspected drug is printed out as well as the phone call registration sheets in order to note down all the attempts performed to get in touch with reporter.

In order to thank the reporter, a response letter is sent back with confirmation of reception and acceptance of the report. To encourage reporting, 2 blank reporting sheets are sent too.

In situations related to quality problems detected without ADR, the reports are not inserted on SVIG. In any case, the reporter is also contacted and advised to report quality problems to DIL and, if available, save a sample of suspected drug to aftermost analyses.

For each report, a telephone contact is performed to check or to get missing information about the case. When talking directly to the reporter is not possible, the confidentiality of the reporter, drug and patient is always assured. Sometimes, by reporter request, electronic mail is used to perform the contact. All data recorded is added to the SVIG. After that, a summary of the report is written as a narrative and the case is closed. An email is sent to

INFARMED to inform that data entry is completed. The essential information to perform the causality assessment has to be collected and entered on SVIG within 7 days after reception of report. On the following causality attribution meeting, the clinical coordinator performs the causality assessment of ADR through a process of global introspection which takes into consideration several factors as the temporal relationship, pharmacological plausibility, concomitant drugs and rechallenge. Then, the decision is shared with the reporter (36-37).

In order to have an administrative control, RPULVT has a database "Reports characterization List" where the most important characteristics of notifications are registered.

During this process, notifications are organized as:

1. Pending contact
2. Causality already assessed
3. Unprocessed notifications by RPULVT

3.3.2. Alert Sign Generation

Quality problems suspected with ADR and reported to RPULVT are assessed on the day of reception in order to determine if an alert sign should be emitted to Inspection and Licensing Department (DIL), an INFARMED department. In these cases, when the reporter is contacted, special attention is given to the existence of any sample of the drug suspected lot which could be used for foremost analyses.

A signal is defined as "information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judge to be of sufficient likelihood to justify verificatory action" (38).

Those reports received without ADR are not processed through RPULVT.

3.3.3. Educational interventions

However, the RPULVT's responsibilities are not only to process ADR reports but also to get closer to health care professionals in order to make them aware of cooperation with the Pharmacovigilance System importance to public health.

Although spontaneous reporting is the most used method to detect ADR with some many advantages like including the entire population, all marketed drugs and during their whole life cycle, detect rare ADR and being a cheap method, it presents a huge disadvantage: the rate of reporting is rather low which means there is clearly a lack of information (38).

To face up this challenge, educational interventions have been performed. A study conducted by Prof. Adolfo Figueiras shows physicians reporting rate increases after intervention and reaches a maximal effect in the first 4 months after the intervention, but the magnitude of the effect decreases in subsequent periods, remaining significant up to 1 year as it is possible to see in Figure 17. The intervention also led to an improvement in the quality of reports by increasing the reporting rate for serious, high causality, unexpected and new ADRs (38).

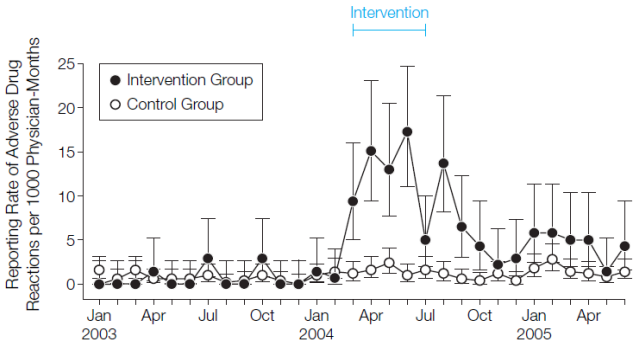


Figure 17: Impact of an intervention on the reporting rate.

Source: Reproduced from Figure 2 of ref. 38.

During my internship in RPULVT, I also could visit a hospital pharmacy and observe how these interventions are made in order to encourage pharmacists to report ADR. The outreach visit consisted of a presentation that addresses some definitions of pharmaco-surveillance and ADRs reporting; conclusions obtained in international studies and the cost

of ADR to health systems and patients. The methods used in spontaneous reporting systems are also described. The underreporting rate is presented as the system's principal limitation through the presentation and could be decreased by taking only 5 minutes to complete the report forms.

When visiting some healthcare professionals for the second time, that showed to have still a positive impact. As shown in Figure 18, comparing baseline reporting in this study with the one conducted in 2004 (Figure 17), the rates, although similar, were a little higher in 2008, which suggests that the effect of outreach visits improve the reporting rates in a long term. So, it seems useful to keep on performing educational interventions (39).

Reporting	Group	Period						
		Baseline	Post-intervention					
			Overall period	4-month period				
				First	Second	Third	Fourth	Fifth[b]
Overall	Workshop intervention	10.41 (10)	52.74 (39)	63.58 (20)	15.89 (5)	12.71 (4)	19.07 (6)	11.57 (2)
	Telephone intervention	19.89 (49)	22.73 (40)	17.05 (12)	9.94 (7)	8.52 (6)	7.10 (5)	28.41 (10)
	Control	10.28 (122)	11.96 (102)	4.08 (14)	6.12 (21)	3.50 (12)	10.21 (35)	11.56 (20)
Serious	Workshop intervention	3.12 (3)	21.64 (16)	25.43 (8)	3.18 (1)	6.36 (2)	12.72 (4)	0 (0)
	Telephone intervention	15.02 (37)	14.20 (25)	12.78 (9)	5.68 (4)	5.68 (4)	4.26 (3)	14.20 (5)
	Control	6.99 (83)	7.51 (64)	2.62 (9)	2.33 (8)	3.21 (11)	5.54 (19)	9.83 (17)
Unexpected	Workshop intervention	3.12 (3)	6.76 (5)	6.36 (2)	0 (0)	3.18 (1)	3.18 (1)	0 (0)
	Telephone intervention	3.24 (8)	3.98 (7)	1.42 (1)	4.26 (3)	1.42 (1)	1.42 (1)	2.84 (1)
	Control	1.60 (19)	2.35 (20)	0 (0)	1.46 (5)	0.87 (3)	2.33 (8)	2.31 (4)
High-causality	Workshop intervention	6.25 (6)	36.51 (27)	47.68 (15)	12.72 (4)	9.54 (3)	12.72 (4)	0 (0)
	Telephone intervention	14.61 (36)	15.91 (28)	8.52 (6)	9.94 (7)	7.10 (5)	4.26 (3)	19.89 (7)
	Control	6.41 (76)	9.85 (84)	3.50 (12)	4.67 (16)	2.62 (9)	9.04 (31)	9.25 (16)
New drug-related	Workshop intervention	4.16 (4)	13.52 (10)	12.72 (4)	6.36 (2)	6.36 (2)	3.18 (1)	5.78 (1)
	Telephone intervention	3.25 (8)	3.41 (6)	5.68 (4)	1.42 (1)	1.42 (1)	0 (0)	0 (0)
	Control	3.88 (46)	5.75 (49)	2.33 (8)	4.08 (14)	1.46 (5)	4.08 (14)	4.63 (8)

a [(No. of reports of a study group during a specific follow-up period (months))/(no. of physicians belonging to the study group during that follow-up period)∗(no. of months in that follow-up period)]∗1000∗12.

b Follow-up of all subjects was not complete.

Figure 18: ADR reporting rate per 1000 physician-years categorized by adverse drug reaction type and period, pre- and post intervention.

Source: Table II of ref. 39.

I also had the opportunity to participate in an Intensive Course of Pharmacovigilance for health care professionals. During this course, I attended several presentations regarding a wide range of medical specialties which discussed the most frequent ADR in each of them.

3.3.4. Applications to research projects

During my internship in RPULVT, I also had the opportunity to prepare 2 applications to research projects:

An Expression of Interests promoted by EMA

This call aimed to identify potential contractors interested on being invited for future drug safety studies. For this, we had to join the team CV's, a list of main observational drug safety studies performed in the last 3 years, a list of recent publications about studies performed, research facilities and data sources which could be analysed and the conclusion that could be achieved.

ENCePP Task Force on HTA on Health Technology Assessment (HTA)

This is a scientific research addressing the economic, organizational, social, and ethical impacts of pharmaceuticals, devices, diagnostics and treatments, and other clinical, public health, and organizational interventions. The aim was to provide best evidence to policy and clinical decision-makers responsible for the introduction and assimilation of health technologies in national health services. In this application we had the opportunity to express our scientific interests as well as previous works and facilities available which could be useful for future partnerships.

3.3.5. Writing a retrospective observational database study protocol

Another great opportunity I had at RPULVT was to design and present pharmacoepidemiological studies protocol. Pharmacoepidemiological studies reflect the patterns of drug use and their subsequent effects in the population. These studies looked to achieve several targets such as, for example, the optimised rational use of drugs, not only at the individual level but at the clinician's and at the pharmacist's level as well, in order to avoid all of the different drug concerning problems that have appeared in a large extent during the last decades (ADR's, drug-drug interactions, drug resistance, noncompliance, unadvised self-medication, the concurrent use of contraindicated drugs, prescription and filling errors, the unpredictable outcomes resulting from the use of drug in population's frail groups as infants, elderly and pregnant women, and the therapeutic regimens conceived for the mass).

Consequently, I wrote a protocol for a review of the Portuguese Pharmacovigilance database regarding the neuropsychiatric adverse drug reactions.

The aim of this retrospective observational study was to analyze all the adverse events reported after the administration of drugs for neurological and psychiatric indications and the neurological and psychiatric adverse events reported after the administration of any drug regarding demography, seriousness, type (system organ class) and suspected drug in order to give an idea to neurologists and psychiatrists of the most common ADR.

The conclusions of this study will be used to make neurologists and psychiatrists aware of the importance of reporting in future educative interventions.

I also prepared the protocol and Ethics Committee form to be submitted to Hospital Ethics Committee. At the end of my internship we were still waiting for the response.

4. Discussion

My internship in a research institute that was linked to a school of medicine and a hospital, gave me the opportunity to see the translational medicine concept put into practice "from bench to bedside and from bedside to bench again". I was able to confirm the proposal of clinical trials that came from the industry through CRO's while, on the other hand, physicians generated new ideas and wrote them down as a protocol and conduct them as clinical or observational studies.

This was, undoubtedly, a very enriching experience. I had the opportunity to be involved in a) the quest for funding to support interesting research ideas, b) the writing of an application for a research project and a protocol for a database analysis for ADR, c) the coordinating of several activities required *per protocol* in a number of clinical trials and observational studies, d) the preparing and submitting of scientific articles and e) the processing of ADR reported spontaneously to Pharmacovigilance National System. In summary, I experienced several stages involved in the research procedure which has allowed me to learn and grow professionally and personally.

Since the first moment of my experience at NCRU, I began to appreciate the effort for study procedures to be strictly followed and documented. One gold rule in clinical trials is "what is not written, it is not done". The team balance/organization achieved was truly impressive. I also recognized being a study coordinator is, actually, much more than ensuring protocol details are followed or entering data. The SC plays a pivotal role by managing the anxieties and expectations of patients with the clinical research, assisting clinical monitors and facilitating the communication between investigators, patients and monitors.

Regarding the neurology field, I found out many of the larger companies in the pharmaceutical industry have made dramatic cuts in worldwide research investment in this area. The reasons presented involve the limited understanding of the brain, its molecular and cellular mechanisms and the disease complexity which avoid a profitable drug development concerning the clinical trial dependence on soft behavioral endpoints and the

inexistence of established biochemical surrogate markers (40). Actually, the development of Central Nervous System (CNS) drugs is longer than for other therapeutic areas and the rate of success is lower. However, this is a therapeutic area where the need for drugs is still marked. Recently, a Nature article stated that 13% of the global burden of disease is attributable to mental, neurological and substance abuse disorders (41). I have started to better understand the difficulties pharmaceutical research is currently facing.

A special point I learnt related to preparing the monitoring visit is that it should begin on the day patient comes to the visit in order to avoid protocol deviations. In addition, the monitor is someone available to help and cooperate with us. Usually monitors understand the study coordinators efforts and they are always available to assist in those areas of special concern.

Due to the privilege of having played both roles as clinical study coordinator and clinical monitor, I had the opportunity to understand both the expectations of a monitor regarding the site team and, at the same time, the challenges that a study coordinators faces in the routine site. This was one of the main positive aspects of my internship.

The science management task was the field where I learnt the most. In the beginning, I saw the funding grants as a support tool not as a goal itself. However, nowadays getting science support is a top priority. Furthermore, grants with specific objectives and explicit deliverables can only be applied to those types of research projects where the underlying principles are already well known and the deliverables can be reasonably specified in advance. This means paradigm-shifting works, by default, cannot get funds directly based on project proposals since innovative ideas have no precedents and consequently peers cannot fully understand what they are about (42).

In the science writing process, I have recognized that we have to practice writing and thinking about writing to succeed. We can learn with the example of others writing. Our ability to express our ideas is enhanced as we read the scientific literature and see how professional scientists write about their work. Something which helped me most was to repeatedly practice reading, writing, and constructively criticizing other's writing.

Being at a Regional Pharmacovigilance Unit after having acquired some experience as study coordinator, made me strongly appreciate the importance of all the information AE/SAE forms require. As a study coordinator, I have noticed these forms are quite extensive and too detailed. However, when I saw all the details that were taken into account to make the causality assessment, then I understood why it was so important to have so much detailed information. Only at this point I perceived how important each field was to make a correct judgment.

To summarize, getting closer to these 4 areas allowed me to see how they are interconnected with each other. My experience as clinical monitor helped me understand the importance of doing things in a specific way as a study coordinator and vice versa. The Pharmacovigilance procedures helped me value the effort to obtain all the information related to safety in Clinical Trials and the Science Management has given me an idea about the aspects surrounding the clinical research. Actually, being involved in these 4 areas gave me a clearer picture of the clinical research itself.

Another big advantage I took from this experience was the working methods and habits I learnt. The whole team always demonstrated will to teach me and to share their working habits and their professional achievements with me, even in topics that I was not able to generate questions/doubts by myself. I benefited from professionals who brainstormed with me and I highly appreciated it.

During my internship, all the opportunities I found for improvement are only suggestions and future desires for this institution which kindly hosted me so well. They include:

- Referring to the NCRU, I think the most meaningful change to do might be to establish a closer workflow with pharmacy department. Even though we receive a timetable with the scheduled visits for the whole week, it is common to find a patient waiting for investigational medicines more than half-an-hour. In addition, I think there might be a great benefit to see more commitment from those responsible for the approval of clinical trials in the hospital. There are clear advantages of

bringing the trials to the hospital, not only financial but also the opportunity health professionals have to present new chances of treatment to patients.

- Regarding Pharmacovigilance and taking advantage of the data collected from the reports, I believe it would be beneficial to see more database analyses being performed. Doing this, I believe the whole team would see, in practice, the importance of continuous collecting and processing every detail of each report.
- For the science management, I think there are several things which could be done. A support facility close to the investigators could provide services like writing periodic reports, reviewing and submitting scientific articles, coordinating and submitting applications for bigger projects. I really believe having someone responsible for this, would make investigators more available and dedicated to the research activities while the submission procedures would be facilitated. This would result in more successes and productivity in a medium/long-term.

One of the great challenges I faced was time management. When I arrived I wanted to see everything, how it was done and how it fits in the daily routine. But quickly, doing effort management became a goal. Also situations such as “please, do this when you have time to” were another challenge. To overcome this, I began setting a deadline in my head to finish each task.

5. Conclusions

Clinical research is, in fact, more than a career or a job. Now, I nurture a deep admiration for all those who devote their lives to scientific discoveries. Research requires unconditional commitment, enthusiasm and inspiration. There are several other endeavors that yield more secondary gains such as financial rewards, recognition and an easy-going life for practitioners. So, I found myself so many times, thinking how important these efforts are for the society, although most of them are invisible to those who benefit from them.

Additionally, my internship has become more than I have ever expected. From the opportunity to follow several clinical trials in different stages, for different indications, with different requirements to the wide range of people I contacted: the different sponsors and clinical monitors with different work methods to the patients and participants willing to contribute to the increasing of scientific knowledge, without forgetting the health professionals I interacted with (study coordinators, pharmacists, physicians, science managers, nurses and laboratory technicians). The contribution of all these members made my curricular internship really significant and helped me to achieve all the proposed objectives.

This ten-month experience was really remarkable: not only because IMM is a reference for science in Portugal but also due to the different work situations I experimented and the working habits I acquired. I had opportunity not only to put into practice those concepts learned previously and new ones but also develop a great range of professional skills in a so short period. I now feel much more confident with a more practical idea of what is really clinical research and I am ready to take up new challenges in my future career. But having the opportunity to perform such a varied range of activities was very useful not only for my professional growth but also for my self-knowledge. Today, I am more aware of my strengths and weaknesses. I can now say that I have a much more realistic view of what scientific research means.

I am deeply grateful for being invited to continue my activities initiated as science manager of the principal investigator, the position I enjoyed the most. I really appreciated the opportunity to learn with this high level team and having a chance to continue learning and working next to those that I ultimately admire a lot.

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