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**ESTÁGIO EM GESTÃO DE DADOS E ESTATÍSTICA
NUMA *CRO***

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Relatório apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde

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palavras-chave Estágio, CRO, Investigação Clínica, Gestão de Dados, Bioestatística, Biomedicina Farmacêutica, KeyPoint.

resumo Este relatório tem como objectivo descrever o meu estágio em Gestão de Dados e Bioestatística na Keypoint. Este estágio foi um complemento prático do Mestrado em Biomedicina Farmacêutica e este relatório de estágio serve como tese do segundo ano curricular do referido mestrado.

Este estágio de 9 meses na Keypoint incluiu actividades de todas as fases dos serviços de Gestão de Dados e Estatística, em diferentes projectos. Estes projectos abrageram ensaios clínicos e estudos observacionais, com medicamentos e suplementos alimentares, e ainda uma tese de pós-graduação não relacionada com investigação clínica. Incluiu também um projecto que tinha como base a realização de entrevistas. Foi possível ainda participar em várias formações, nas áreas de *medical writing*, dispositivos médicos e entrevistas. Esta experiência permitiu não só desenvolver competências técnicas em Gestão de Dados e Estatística mas também ajudou a desenvolver soft-skills e perceber melhor a realidade da investigação clínica em Portugal.

abstract

This report aims to describe my internship in Data Management and Biostatistics in Keypoint. This internship was a practical complement to my theoretical education in the Masters in Pharmaceutical Medicine and this reports serves as a thesis to the 2nd year of the mentioned Masters.

This 9 months internship in Keypoint focused in activities of all stages of the services of Data Management and Biostatistics provided by Keypoint, in several different types of projects. These projects covered clinical trials and observational studies, with medicines and food supplements, and a post-graduation thesis in an area not related to clinical research. The internship also included a project that was based on the conduction of interviews. There was the chance to several trainings in the areas of medical writing, medical devices and conduction of interviews. This experience allow me to not only develop hard skills in Data Management and Biostatistics but also to further soft-skills and to better understand the reality of clinical research in Portugal.

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Abbreviation List

ATC: Anatomical Therapeutic Chemical

CEIC: *Comissão de Ética para a Investigação Clínica*

CNPD: *Comissão Nacional de Proteção de Dados*

CRA: Clinical Research Associate

CRF: Case Report Form

CRO: Contract Research Organisation

CTA: Clinical Trial Assistant

DVP: Data Validation Plan

eCRF: Electronic Case Report Form

EMA: European Medicines Agency

INFARMED: *Autoridade Nacional do Medicamento e Produtos de Saúde I.P*

IT: Information Technologies

IWRS: Interactive Web Response System

MAH: Marketing Authorisation Holder

R&D: Research & Development

SAP: Statistical Analysis Plan

SOP: Standard Operating Procedure

1. Introduction

This report presents a summary of my internship in Keypoint CRO, where I worked from September 2012 to May 2013, as part of the curricular internship for my thesis in the 2nd year of the Master Degree in Pharmaceutical Medicine at the University of Aveiro.

Keypoint CRO, hereinafter Keypoint, is a Full Service Contract Research Organisation (CRO), based on Miraflores, Lisbon, which provides scientific support in clinical research to pharmaceutical industry, academic institutions, independent investigators and post-graduate students (1).

My internship was mainly focused in the areas of Data Management and Biostatistics. Nevertheless, I had the chance to have several trainings and to participate in other activities such as conduction of surveys.

The goal of this report is to describe my activities during the internship and to state what I learned, what I appreciated the most, my biggest difficulties and how I overcame them, how the Master was essential to perform the internship tasks and to forecast how the internship will be useful for my future career.

To provide start, there is a section stating the internship objectives and an introduction to the company. Then, there is a description of the current state of the art of clinical research, together with the applicable regulatory framework in the European Union and in Portugal, and with the importance of the services of data management and statistics. Afterwards, it is provided an analysis of these topics in Portugal. Then, it is described which activities I performed in which area and then a section where I discuss what I have learned. In the end, there is a conclusion that summarizes the whole report.

1.1. Overview of the Host Company

Contract research organizations are companies that provide scientific support to pharmaceutical companies and academic institutions in several fields of clinical research. They can provide a wide range of services in all stages: study design, protocol planning, subject recruitment, monitoring, data management, statistics, medical writing, pharmacoeconomics, pharmacovigilance, regulatory affairs, project management, etc (2).

Keypoint was founded in 1999 as a scientific consulting company and soon (2003) it started expanding its working areas to epidemiology, data management and medical writing (1). Then, in 2004, Keypoint started working with clinical trials and obtained the certification ISO 9001. In 2005, Forpoint, a branch for training purposes, was created. In 2006, Keypoint created a new branch called Point2Point – New Scientific Solutions in Health Point2point with the goal to develop creative and tailored support in the areas of disease prevention and disease and health promotion. It also had focus on product marketing. However, due to the Portuguese economic crisis and the company subsequent restructuration in 2007, this branch was closed. Currently, Grupo Keypoit is composed of Keypoint which is a full service CRO which acts on clinical trials, observational studies, epidemiologic studies, economic evaluation, medical writing, data management, statistics and Forpoint with training and education purposes (1). In Figure 1, it is possible to see the organisational chart of Keypoint by the time of my internship (3).
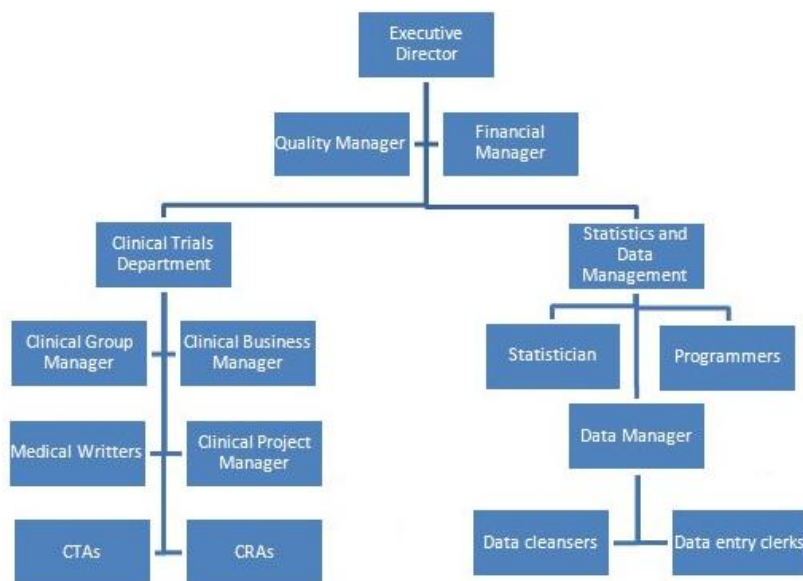

Figure 1 - KeyPoint CRO Organisational Chart

CTA: Clinical Trial Assistant; CRA: Contract Research Associate (3)

In the clinical trials area, Keypoint provides services like research documents elaboration (e.g., protocol and case report form (CRFs)), feasibility studies, clinical trial application submissions, project management, monitoring, data management, statistics and medical writing. The main therapeutical area is oncology (36% of the total number of clinical trials) but Keypoint it works with all other therapeutic areas (1).

Regarding observational studies, Keypoint provides almost the same services as for the clinical trials. These types of studies are the main studies dealt by Keypoint. The most common therapeutical areas are oncology (21%) and nephrology (19%) (1).

For epidemiologic studies, Keypoint collaborates in the development of study protocols and questionnaires, sampling, surveys, data management, statistics and medical writing. For this type of studies there is no main therapeutical area, as they have almost the same frequency (1).

In economic evaluation, Keypoint provides support in the economic evaluation of medicines and medical devices, elaboration of economic models, conduction of panels of experts and marketing support. The main therapeutical area is oncology (45%) (1).

For general medical writing activities, Keypoint develops documents like abstracts, posters, articles and also conducts translations. The main area is also oncology (34%) (1).

For general data management and information technologies (IT) activities, Keypoint provides services like development of CRFs (both in paper and electronic version), elaboration of data validation plans, design and maintenance of databases, collection of data, data entry support, maintenance of interactive web response systems (IWRS), data validation and queries generation (1).

For general statistics activities, Keypoint provides services like support to general protocols development (e.g., endpoints and statistics methodology), development of randomization lists, calculation of sample size, development of statistical analysis plans and statistical reports (1).

In resourcing, Keypoint provides human resources like clinical research associates (CRAs), clinical trial assistants (CTAs) and project managers to pharmaceutical industries (1).

In total, since its foundation until the time that I have terminated the internship, Keypoint has worked in more than 600 projects, across more than 30 therapeutical areas, both at national and international level. The main types of services provided, in terms of number, were observational studies (60%) and medical writing activities (25%). The most frequent

therapeutical areas were oncology (26%) and nephrology (13%). Keypoint has a wide range of types of clients like pharmaceutical industry, alimentary industry, international CROs, hospitals, universities, doctors and post-graduation students (1).

ForPoint (Instituto de Formação e Inovação na Saúde) is a branch of GrupoKeypoint, without lucrative goals and with focus on professional training in clinical research and promotion of health education in society. It offers post-graduate courses in clinical research and other short courses in specialized areas like clinical trials, biostatistics, data management, statistics, medical writing and pharmacoeconomics (1).

During my internship in Keypoint I was based in the Data Management and Statistics Department. Here, I worked with statisticians, data managers, data cleansers, database developers, IT technicians and data entry clerks. However, I have also liaised with people from other departments like project managers, CRAs, CTA and medical writers and with people from outside the organization, like investigators.

In Keypoint, the Data Manager and the Statistician are both involved in the studies since its beginning as they cooperate in the development of the protocol and the CRF. Then, the Data Manager develops the data validation plan (DVP) while the Statistician works on the statistical analysis plan (SAP). After that, the Data Manager develops the database in Microsoft Access© or in an electronic case report form (eCRF) platform, in this case with the support of IT. After the CRFs are filled by the investigator and reviewed by the CRA, they are brought to Keypoint, where there is a passage of service between the CRA and the Data Manager (data transfer document, which both sign). Afterwards, the Data Manager briefly reviews the CRFs again to guarantee that they are ready to be inserted by the data entry clerks, who proceed to the data entry process. Afterwards, the Data Manager starts the data cleansing process and locks the database. Then, the statistician elaborates the statistician report. After this the report is concluded, the CRFs are archived, according to the national and international requirements. In Figure 2 it is possible to see the flow of procedures in Data Management and Statistics in Keypoint.
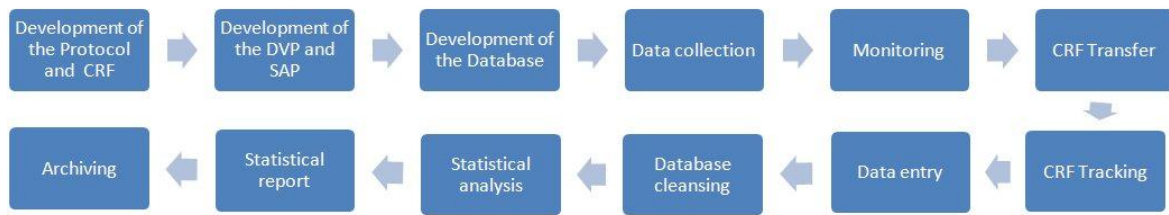
Figure 2 - Flowchart illustrating the procedures in Data Management and Statistics in Keypoint
CRF: Case Report File; DVP: Data Validation Plan; SAP: Statistical Analysis Plan

1.2. Objectives

My main objective for this internship was to further my knowledge and experience in Data Management and Statistics in the field of Clinical Research:

- Learn how to develop databases for clinical trials and observational studies;
- Implement the theoretical statistical knowledge from the Masters in real statistical analysis reports;
- Understand the interaction between the data management activities with the statistical activities in a CRO.

As additional objectives I wanted to:

- Understand better the role and importance of a CRO in the field of clinical research;
- Learn about the daily work routine of a CRO;
- Develop soft skills such as communication skills, team-work, responsibility, autonomy, time management, and prioritization;
- Apply what I learned in the Masters in a real life scenario;
- Grow not only as a professional but also as a person.

1.3. State of the Art of Data Management and Statistics in Clinical Research

This section will define clinical research and its legal framework. Then, it will focus on the importance of Data Management and Statistics in clinical research. To conclude, it will describe the state of the art of clinical research in Portugal.

Clinical research can be generally defined as any research that involves people or uses materials from human like their behaviour or biological samples (4).

Clinical research was classically divided in clinical trials (interventional studies) and observational studies (non- interventional studies). Then, clinical trials were divided by the stage of development (from Phase I to Phase IV) and observational studies were divided by their methodology (cross-sectional studies, cohort studies and case-control studies) (5).

Phase I studies are the ''first-in-man'' studies. Despite for some conditions (e.g., cancer) there are patients involved, this type of studies is usually conducted in healthy volunteers and they   don't involve a high number of subjects (just a few dozens). The main endpoint measures are ADME (absorption, distribution, metabolism and excretion) as well as some safety parameters. The main purpose of these studies is to determine the most appropriate and safe dose for Phase II (5). Phase II studies aim to find out which is the best therapeutic dose with the less adverse reactions, in order to define the dose regimen for next phase trials. These studies already involve patients and it can reach a few hundred subjects (5). The Phase III trials aim to prove or confirm therapeutic benefit as well as the safety profile of the medical product. These studies are the main basis for the approval or rejection of the marketing authorization by the regulatory authorities. They are conducted in a population very similar to the real one and they usually have thousands of subjects (5). After the marketing authorisation is granted, the marketing authorisation holder (MAH) can conduct Phase IV either voluntarily or by imposition of the regulatory authorities. These studies can be very diverse and their purposes can be a better characterization of the safety profile or addition of new indications or patient populations (5).

Also, clinical trials can also be divided according to its goal in Human Pharmacology studies, Therapeutic Exploratory studies, Therapeutic Confirmatory studies and Therapeutic Use studies (5). Human Pharmacology studies aim to assess tolerance, characterize pharmacokinetics and evaluate interactions with other medicinal products or

food. The goals of the Therapeutic Exploratory studies are to estimate dosage and decide study designs and endpoints for future studies. The therapeutic confirmatory studies aim to demonstrate efficacy and characterize the safety profile, in order to support the marketing authorisation. The purpose of the therapeutic use studies is to detect less common adverse reactions and better understand the safety profile of the medicinal product (5).

However, with the progress of science and the correspondent evolution of the regulators, these definitions changed recently in the European Union. So, according to the new Clinical Trial Regulation, currently there are two types of studies: the clinical studies and the clinical trials (6). A clinical study now is defined as any investigation relating to humans, involving one or more medicinal products, with at least one of the following intentions:

- Discovering or verifying the clinical, pharmacological or other pharmacodynamic effects;
- Identifying adverse reactions; or
- Studying the absorption, distribution, metabolism and excretion properties;

with the purpose of assessing the safety and/or efficacy of those medicinal products (6).

On the other hand, a clinical trial is a clinical study if it fulfils at least one of the conditions:

- the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
- the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or
- diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects (6).

The pharmaceutical industry is one the most highly regulated industries which is understandable considering the population exposed to medicines (2) (7). This way, clinical trials (and observational studies, in a lesser extend) are much regulated. There are national and international laws and guidelines regarding clinical research. The international laws, in Europe, can be regulations or directives. European regulations are European laws that are legally binding in all Member-States while European Directives must be transposed to the

national law of each Member-State (8). The following list briefly describes the main European Directives and Regulations relating to clinical research:

- Directive 2001/20/EC, of 4 April 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (9);

- Directive 2005/28/EC, of 8 April 2005, laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (10);

- Directive 2010/84/EU, of 15 December 2010, amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (11);

- Directive 2012/26/EU, of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance (12);

- Regulation (EC) No. 726/2004, of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (13);

- Regulation (EU) No. 1235/2010, of 15 December 2010, amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (14);

- Regulation (EU) No. 1027/2012 of 25 October 2012, amending Regulation (EC) no 726/2004 as regards pharmacovigilance (15);

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (13).

The following list describes the main Portuguese laws regarding to clinical research:

- Law n. 46/2004, from 19 August, approves the set of regulations regarding to the conduction of clinical trials with human medicines (16);

- Decree-Law no. 176/2006, from 30 August, *"Estatuto do Medicamento"* - states the main regulations regarding manufacturing, quality control, safety and efficacy, market authorization and marketing of human medicines (17);

- Decree-Law no. 102/2007, from 2 April, implements Directive 2005/28/CE (18);

- Law n. 21/2014, from 16 April, approves the regulations regarding clinical research (19).

Also, there are several non-binding ethical documents which are very important in clinical research. The biggest example is the Declaration of Helsinki which is a document elaborated by the Worlds Medicine Association which states the ethical principles that investigators in clinical research should abide (20).

There is also a set of guidelines which are also not legally binding but provide invaluable support in clinical research. The most relevant are the ones elaborated by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and its most used guideline is probably the E8 – Good Clinical Practices which states the principles of clinical research (5).

The current clinical research regulation is based on the legal and ethical requirements mention above. However, the pharmaceutical world is an ever-changing industry and legislation is always required to address new issues and expectations for all the stakeholders. In this context, new sets of regulations have been released recently like the Pharmacovigilance Regulation (i.e., Directive 2010/84/EU and Regulation No 1235/2010) and the Clinical Trials Regulation (i.e., Regulation No 536/2014) (11) (14) (13). To address these change it is essential to have professionals with proper education not only based in hard skills as these can change, but also on soft skills that allow them to adapt to this dynamic regulatory environment.

Data Management starts to be important right before the study starts. In a clinical trial, thousands of data from hundreds of subjects are collected, so proper planning in the data collection methodology is required. The input from the data management team in the development of the protocol is invaluable because it is necessary to choose the type of variables to be collected and to define the type of database to be used. This also impacts the type of CRF (paper or electronic version). While the study is going on, it is necessary to maintain the database, insert CRFs in the database and deal with queries that will be generated. When the study ends, or when an interim analysis is required, it is necessary to lock the database, perform data cleansing data for duplicates and data entry mistakes and prepare the data for the statistical analysis.

Statistics also play an essential role right from the beginning of the trial. The input of a statistician is essential to define the variables, design of the study, sample size, power of the study. Then, the statistical team are useful again when the study ends (or when there is an interim analysis) where they elaborate the trial or the clinical trial report.

There are several software programs that support the tasks of Data Management and Statistics in clinical research. For data management, Microsoft Excel® and Microsoft Access© provide support for the simpler studies. For more elaborate studies like clinical trials, eCRF platforms like Oracle can provide more professional tools for the tasks required.

For Statistics, Microsoft Excel® can provide very basic tasks but it is not very used due to its statistical limitations. The most common software in statistics programs are the IBM SPSS Statistics™, Stata™, Epi Info™, R™ and SAS™. Epi Info™, STATA™ and R™ have the advantage of being freeware. R™ and SAS™ are more customizable and versatile software programs and, consequently, are not so user friendly and require more trained staff. SPSS™ is a simpler but paid option.

The trend of clinical research in Europe is changing, In general, pharmaceutical companies are moving their clinical trials to the Eastern European countries (like Ukraine or Romania) or even out of Europe, since these countries are getting the required conditions to the conduction of clinical trials at lower costs (21). Portugal is no exception to this diminution in the number of clinical trials; however, Portugal has less than 55% of the clinical trials of countries of similar dimensions, like Belgium (22) (23).

The number of submitted clinical trial applications almost halved from 2006 (160 clinical trial applications) to 2011 (88 clinical trial applications). Consequently, the number of authorized clinical trial applications also lowered (from 147 to 87). This can be seen in Figure 3, which shows the number of clinical trials application submitted to Autoridade Nacional do Medicamento e Produtos de Saúde I.P. (Infarmed) from 2006 to 2013 (24).
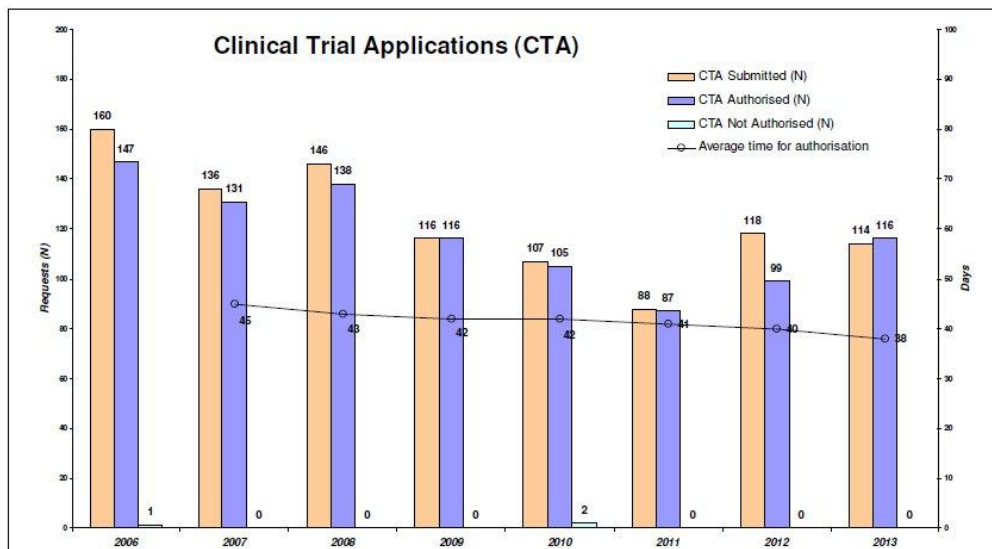

Figure 3 – Clinical trial applications to Infarmed 2006-2013 (24)

This decrease can be partially explained by the closing of the Research & Development (R&D) Units of some pharmaceutical companies (e.g., GlaxoSmithKline and Lilly) in Portugal, which led to even less clinical trials (25). However, the last two years (2012 and 2013) show positive signs of recovery. It is also possible to see a decreasing in the time for the Infarmed's evaluation and approval (from 45 days in 2007 to 38 days in 2013, decreasing almost every year). Regarding the clinical trial applications statistics by Anatomical Therapeutic Chemical (ATC) Classification System, "Antineoplastic and immunomodulating agents" keep being the most prevalent therapeutical area, which is

concordant with the international trend. Then, "Antiinfectives for systemic use", followed by "Cardiovascular". Traditionally, until 2012, the third most prevalent category in clinical trials in Portugal was "Nervous System", so this marks slight change in the main therapeutical areas (24).

Regarding the clinical trial phases, we can see in Figure 4 that it hasn't changed much. Phase III clinical trials are still the most prevalent phase in Portugal, followed by some Phase II clinical trials and, in a lesser extent, Phase I and IV trials. Nevertheless, it should be pointed out that in 2013 was the year with the highest number of Phase I trials so far (24).
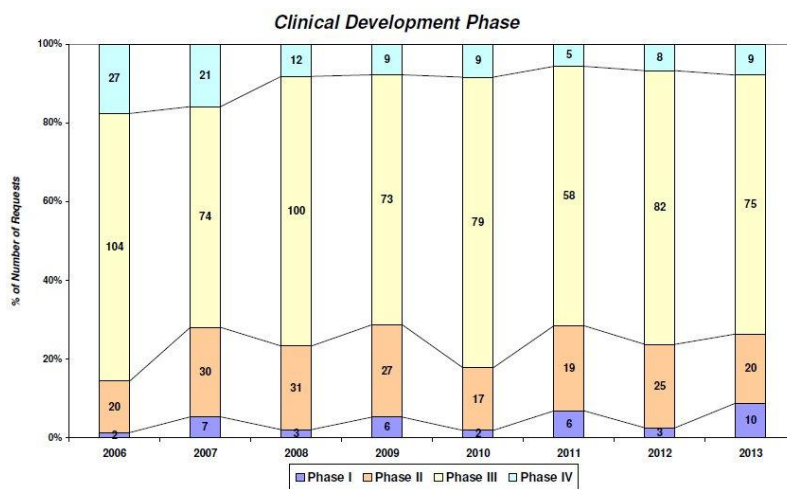
Figure 4 – Clinical trial applications by study phase 2006-2013 (24)

About the type of sponsor, as it is possible to see in Figure 5, the trend continues to be industry sponsored studies. However, it is also worthy to point out that in 2013 it was the year with the most academic clinical trials so far (16 trials, representing 14% of the total number of clinical trials). This value represents an increase over 100% compared with the last three years (24).
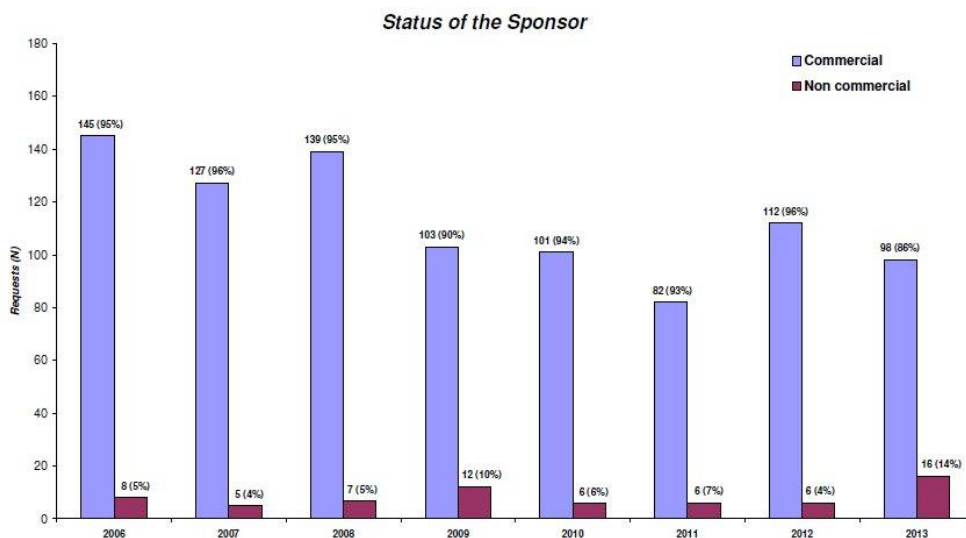
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Figure 5 – Clinical trial applications by sponsor type 2006-2013 (24)

Because of the mentioned decrease in the number of clinical trials, Portugal was losing 135 million euros per year that could be invested in the health facilities where clinical trials are conducted. Additionally, the investment in clinical research has been diminishing in the last years (23). The major consequence of less clinical trials is that patients do not benefit to the innovative treatments so quickly (26). Additionally, patients do not benefit from information regarding their diseases and alternative treatments, which are provided in clinical trials (22). Furthermore, the patients lose an opportunity to benefit from a general better treatment since in clinical trials doctors and nurses are subjected to very tight protocols requirements (23).

Another consequence is less financial resources available for health facilities. This involves not only the direct payment, but also the indirect costs (e.g., complementary diagnosis methods, experimental and standard treatment, some equipment to the facilities, etc.) (23). Clinical trials also allow the access to advanced scientific and technologic knowledge to the hospitals. Another important asset if the continuous training of health personal in the several clinical research areas (22).

Moreover, since pharmaceutical companies are shutting down their R&D Units in Portugal there are less qualified professional jobs in this area (23).

There are some constrains to the conduction of clinical trials in Portugal. In Portugal, to start a clinical trial, it is necessary to have the authorisation of Infarmed, Comissão de Ética para a Investigação Clínica (CEIC), Comissão Nacional de Protecção de Dados

(CNPD) and the hospital administration board (25). Infarmed and CEIC have 60 days to review the clinical trial application, however, there is no deadline for the hospitals administrations board. This used to be one of the main issues, as some hospital administrations board took more than six months to provide its approval due to excessive bureaucracy (23). These six months adding to the time of approval of Infarmed and CEIC made the whole approval time almost 8 months (21). This used to lead to situations where the clinical trial was starting in Portugal when it was already ending in other countries, and these situations cause the pharmaceutical companies to lose money (27). There is also great variability in the approval of trials by the centers. In one trial, there was a difference of 69 days between the fastest center (20 days) and the slowest (89 days). Some center did not even have approved the trial in useful time which negatively affects the Portuguese sites' reputation (28) (27) (29). Also, sometimes there is lack of organization whether at national level as at hospital level and there is lack of communication between investigators (22) (30). Moreover, it is also said that there is lack of public incentives to the health services to cooperate in clinical research (31). Another problem is that Portugal is one of the few countries that have a specialised commission just for data protection (CNPD) which causes further delays in the approval of clinical trials. Moreover, it is generally said that there is lack of political will for the conduction of trials (30, 31).

Another major issue that halted the number of clinical trials was the financial crisis that affected all the Europe, but especially Portugal (21).

However, there are several positive points to mention about clinical research in Portugal. Infarmed and CEIC are compliant with their 60 days deadline for approval of clinical trial applications (21). Additionally, some hospitals (e.g., Hospital de Santa Maria, Instituto Português de Oncologia de Lisboa, Hospitais da Universidade de Coimbra, Hospital de São João) give special focus in clinical research and their approval time for a clinical trial can be as low as 15 days (21). Furthermore, the research centers that exist have excellent professionals (26). One of the reasons for that is a continuous effort for some years in the specific training of professional in the area of pharmaceutical medicine. The Training Programme in Pharmaceutical Medicine from University of Aveiro, aims to provide continuous education for the current professionals and train new professionals in the ambit of pharmaceutical medicine and is considered a PharmaTrain Centre of Excellence.

Portugal also has several national CROs to support clinical research. They can act in clinical trials and observational studies, and participate in the design of studies, elaboration of protocols, monitoring, data management, statistical analysis, medical informatics, medical writing, etc. CROs act as a link between the sponsor and the center and they can work with the sponsor or replace it by working in his representation (25). The Health Cluster Portugal has also an important role in the promotion and organization of initiatives for the innovation, manufacturing and marketing of health products through its large national network with international impact (27).

2. On-the-job training

2.1. Multidisciplinary Activities

2.1.1. Training

During my internship, I had the chance to participate in several training courses. To start, I had the general training on Keypoint rules namely on Standard Operational Procedures (SOPs), Quality Manual and on the SAP software to record working hours.

Then, I had specific training more related to my future tasks. This involved the study of guidelines that would be useful for my Data Management and Statistics tasks (e.g., the ICH E9 – Statistical Principles for Clinical Trials and the EMA Guideline on Missing Data in Confirmatory Clinical Trials) (32). The ICH E9 guideline is essential for anyone working in statistics in clinical research. It starts by presenting general considerations for the whole clinical development programme, like basic definitions and differences between the types of populations and variables. Then, it provides advice on trial design issues like blinding, randomisation, sample size calculation and data capture techniques. There are also considerations for issues that can happen during the conduction of the clinical trial like interim analysis, changes in inclusion/exclusion criteria and sample sizes adjustment. This guideline also provides advice for the data analysis process, like how to deal with missing values and data transformation issues. It also provides advice on statistical reporting and how to present the safety and efficacy data (32).

During my internship I also had to study several protocols and CRFs related to the studies for which I performed Data Management and Statistics task. Furthermore, I had a formal course in Medical Writing organized by Forpoint.

Additionally, I had training about the use of medical devices for the measurement of haemoglobin, ferritin and creatinine for an academic study on anaemia. The study aim of the study was to collect demographic and some clinical information through a questionnaire and the values of the previously mentioned parameters thought the collection of a small sample of blood and posterior analysis with a medical device.

Also, I had training on how to conduct interviews with children for a nutrition study about healthy eating habits.

2.1.2. Surveys

One of my side projects was the conduction of surveys with children regarding a nutrition questionnaire study to characterize eating habits. The study focused on the eating habits of the children before and after a training regarding healthy alimentation. The questionnaire was applied before the training and then, 3 months after the training, and 1 year after the training. My task was to conduct the questionnaire in the children as well as to collect some physical information like height, weight and body perimeter.

The study was conducted in pre-schools in Lisbon and some outskirt areas like Amadora, Cascais, Odivelas, Oeiras, Sintra and Santarém.

Before the surveys started, I received training regarding the questionnaire and its variables, on how to conduct the surveys and how to collect the information regarding the physical variables. Then, I received information about the school where I was supposed to go in that day, its location and the expected number of children to interview (this was not a definitive number, because we could only conduct the survey in children who were given written permission by the parents, and sometimes the children forgot to bring the authorisation). After I arrived to the school, I usually had the teacher waiting for me and we went through the written authorisations. After that was sorted out, we usually arranged it in a way that I only had to deal with one child at time, to make it easier since there would be less and sources of distraction. I usually started to present myself and give a brief description of what I was going to ask, tailored to the children comprehension (i.e., "I am going to ask you a few questions about food, ok?"). Then, I started the questionnaire itself. Since the questionnaire contained several pictures with a lot of colours, it was easy to keep the children's attention. However, there was a section that was very repetitive and sometimes the children got bored. So, instead of formulating the same question over and over, I started by only saying the end of the question (i.e., instead of "do you eat sweets? do you eat pizza?", I started saying "Do you eat sweets? And pizza?"), which lead to more attentive children. After all the questions, I weighted and heightened the children and measured their abdominal body perimeter.

2.2. Monodisciplinary Activities

In Table 1, it is possible to see the 22 projects that I have been involved. For 9 projects I performed data management activities for 5 projects only statistics activities, and in 8 projects I performed both type of activities.

Table 1 - Listing of the projects accompanied during the internship

Name	Sponsor	Study type	Therapeutical Area	CRF Review	Database Development	Data Entry	Data Cleaning	Statistics
Alerta	Industry	Observational	Cancer		X	X	X	
Anemia	Industry	Observational	Anaemia	X		X		
Disfunção Sexual	Investigator	Observational	Multiple sclerosis					X
EMINA	Investigator	Observational	Multiple sclerosis					X
EMPed	Investigator	Observational	Multiple sclerosis					X
EURO2012	Individual	Thesis	Football				X	X
Juntos é mais fácil	Public Institution	Observational	Diabetes					X
KELTICLAN	Industry	Observational	Pain		X	X	X	
Ligue C	Industry	Observational	Cancer				X	X
Mutar	Industry	Clinical Trial	Cancer				X	
PARAVERTEBRAL	Industry	Observational	Cancer	X				
PICO	Industry	Clinical Trial	Ophthalmology			X		X
Portsmab	Industry	Clinical Trial	Cancer			X		
PQRS	Industry	Observational	Cancer			X	X	X
PREVAL	Industry	Observational	Cancer			X		
Probiotics	Industry	Clinical Trial	Immunity		X	X	X	
REMA	Industry	Observational	Cancer				X	X
REPAIR	Industry	Observational	Cancer		X	X		X
SANTAREM	Industry	Clinical Trial	Cancer			X	X	X
SER+	Public Institution	Observational	HIV	X				
Skin	Industry	Observational	Dermatology			X		X
Viver em Equilíbrio	Industry	Observational	Cancer					X

These projects were quite different from each other, since some were clinical trials and other observational studies, some were industry studies and others were investigator started-studies. Regardless of most of the studies involved medicines, I had the chance to participate in a study with probiotics, an epidemiologic study, some quality of life studies and a study about football for an academic thesis. Despite the therapeutical area is not very important from a data management or statistics point of view, it was an enriching

experience to work with several different areas like cancer, diabetes, multiple sclerosis, as it helped me understand which are the most common variables for each therapeutical area.

2.2.1. Data Management

In Keypoint, I had the chance to participate in activities covering all phases of Data Management.

I collaborated in the revision of several CRFs for studies which were still the in approval stage. These tasks implied analysing the wording of the questions and answers in the CRF, the type of answer field (e.g. multiple options to choose, blank fields for open text, and also the position of the text in the form itself). An optimized CRF will facilitate the filling by the investigator and the data entering by the data entry clerk, allowing better quality data, with less queries to be generated and with less data do be cleansed.

I created databases in Microsoft Access© for several observational studies with optimized forms and personalised validation rules to facilitate the data entering process. An optimized form in Microsoft Access© should reflect the paper CRF to the maximum extent but it should also allow an easy typing from the data entry clerk. Validation rules like only accepting dates for the date of birth that match the inclusion/exclusion criteria easily help avoiding typographic mistakes. Also, only allowing the insertion of certain replies instead of free text fields, also reduces the number of mistakes. Other optimisation option, is changing text variables ("yes, no" to numeric "1, 2") in order to speed up the data entry process.

 Also, I developed data validation plans to record the rules for the validation and cleansing of the data. I also created annotated CRFs which are CRFs with the name of the variables in the CRFs fields. This is a very important document because it allows the statistician to know the name of the variable of each field in the database, before they perform the analysis. It also allows an easier consultation of the data in the database.

I entered thousands of CRFs in several databases regarding clinical trials, observational studies and other type of studies. I performed these data entry activities in both Microsoft Access© databases and eCRF platforms.

Additionally, I managed the tracking of CRFs: I was responsible for receiving the CRFs from the CRA, distributing of the CRFs through the other data entry clerks, controlling

which CRFs were already inserted in the database and which ones were moved to the archive.

Also, I performed data cleansing activities in order to prepare the data for the statistical analysis. Firstly, I extracted the data from Microsoft Access© and exported it to Microsoft Excel™ to be cleaned. Then, I used several functions and tools to identity duplicates, blank fields and aberrant values like filters, conditional formatting, If Function, Vlookup Function, "Remove Duplicates" Option and Pivot Tables. Some examples of data quality issues that I encountered were situations where the date of visit 2 was before date of visit 1 or when the height of a child reduced considerably from visit 1 to visit 2.

After that, I imported the data to SPSS™ where I created labels for the variables to facilitate the statistician job. Sometimes, I also needed to merge different databases in Excel™ to be analysed together in SPSS.

Also, I provided training for data entry clerk for the databases that I created. I explained them the validation rules, which type of data should be inserted in which field, how to deal with missing and general hints on how to enter the data quicker.

I also participated in the resolution of queries. When a CRF was incomplete or when it contained mistakes that the CRA did not notice or it was discordant with other CRFs from the same subject, I generated a query which would be sent to the investigator. Then, when he/she replied, I documented the reply and updated the database.

After the end of all the data entry and data cleansing activities, I archived the CRFs in the respective study folders where the CRFs were kept according to the applicable regulations.

In Table 1, it is possible to see all the projects that I have been involved, as well as the tasks that I performed for each project. Some projects, like PQRS and SANTAREM, were already in an advanced staged so I was only able to collaborate in data entry and data cleaning activities. Other projects, like SER+ and Alerta, started during the period of my internship so I was able to participate since the initial stage (i.e., CRF review and database development).

2.2.2. Statistics Activities

My main task in the statistical department was the elaboration of statistical reports. A statistical report is a clinical research document elaborated after the completion of a clinical trial (32). It is generally composed by a cover page with the general study details, a synopsis of the study, table of contents, list of abbreviations, ethical considerations, administrative study information, introduction to the report itself, study objectives, study design (including controls, inclusion/exclusion criteria, treatments, randomization and blinding), efficacy and safety variables, data quality considerations, protocol deviations, analysis of safety and efficacy (with subgroup analysis, if applicable), adverse events, discussion and conclusion. It also includes tables and figures relating to the results of the study and appendices like the protocol, CRF and information related to the investigator and the investigational product(s). Despite it is only concluded after the end of the trial, several sections are prepared in advance, at the time of the development protocol, like sample size, inclusion/exclusion criteria, methodology, description of the variables and endpoints (33). I created reports for clinical trials, observational studies and other studies like an academic study about football for a PhD thesis.

I performed both descriptive analysis of the data as well as inferential analysis. In the descriptive analysis, I characterized the population in study with measures like average, median, standard deviation, maximum/minimum, quartiles, counts, percentages, etc. The choice of these measures was based on the type of variables in study. For continuous variables, if the population was normal, it was possible to use the average and the standard deviation. If it wasn't, it was required to use median, maximum/minimum, range and interquartile range. For discrete variables, the appropriate descriptive measures would be counts and percentages. To complement there measures, I also created several types of charts to illustrate the data like line chart, column chart, pie chart and box-plot.

For the inferential analysis, I performed parametric tests (e.g. T Test for the comparison of averages or the ANOVA test) and non-parametric tests (e.g., Wilcoxon test, Mann-Whitney test and Kruskal-Wallis test), depending on the nature of the data available.

Also, I participated in several meetings with investigators (for investigator-driven studies) and project managers (for pharmaceutical industry studies or academic studies). The goals of these meetings were to review the CRF, understand the clients' goals and expectations

for study, and to handle some additional requests in follow up meetings. Being present in these meeting helped me understood the real requirements from the clients, their expectations and knowledge (e.g., in investigator-driven studies, sometimes, the investigator was not fully decided of what he/she really wanted) and issues that can be raised during the conduction of the study (e.g., request for additional analyses).

In Table 1, it is possible to see all the projects for which I collaborated in the statistical report.

Besides the projects in the table, I also made the statistical report for internal activities like the analysis of the feedback questionnaires regarding a training course in Forpoint.

3. Discussion

3.1. Training

My general training was essential to understand how Keypoint works and what each department does. The reading of certain guidelines and internal SOPs also helped me in my core tasks in the Data Management and in the Statistics Departments. The medical writing course that I attended in Forpoint complemented what I had learnt in the Medical Writing course in the Masters and it proved itself to be very useful when I had to make statistical reports. My training in medical devices wasn't directly useful because in the end I didn't participate in the study, however, it was an interesting experience since it was the first time I handled a medical device with diagnosis purposes. On the other hand, the training in how to conduct surveys was completely essential for my role in the nutrition study, as I will discuss in the next topic.

I didn't have many difficulties in this part of the internship as the BSc in Biomedical Sciences and MSc prepared me quite well to continue my learning in Keypoint. So, even if I was confronted with things that I did not know, I was able to learn them quite quickly.

3.2. Surveys

By mid-internship, I was invited to participate in a nutrition study whose goals were to characterize the eating habits of children before and after they had a brief training course on healthy eating habits. When it was suggested that I could participate in the study as an interviewer, I was quite surprised and apprehensive, as I am quite shy and I always felt that I wasn't very good in dealing with children. Nevertheless, I decided to give it a try and I received training on how to conduct the interviews, how to collect the physical variables (i.e., weight, height, abdominal body perimeter) and how to deal with some expected issues (e.g., temporary lack of attention of the children). After that, I was sent to my first school, together with a more experience interviewer. I felt that I was very lucky, since most of the children seemed very interested in the questionnaire and were quite cooperative. With the time, I started to get more confident and everything went even more smoothly. By the time I finished my internship, I was the Keypoint member that covered more schools and that had performed more surveys.

This activity was a very useful experience as it has improved my social skills, not only with children but also with adults, as I needed to interact with the children's teachers. I had to deal with some complex situations like the lack of interview consent from the parents, children that got easily distracted and children with special needs (i.e., mental, hearing and speech impairments). On a more personal note, I also had the chance to get to know new areas of Lisbon and its outskirts, which I probably would never find out by myself, like some of the social problematic areas. After this experience I feel much more confident to conduct surveys, so I am happy that I had the chance to participate in this project.

3.3. Data Management

My favourite part of my data management activities was the opportunity to be involved in all phases of the data management procedures. I especially enjoyed be involved in the CRF development because I could make slight changes that would facilitate the posterior development of the database and the data entry process. I also enjoy to train other data entry clerks to share with them my experience and because I like to give training in general.

The task that I consider more tedious was the insertion of CRFs because it was a monotonous and tedious task. Despite for some studies almost all the staff collaborated, I was the main responsible for data insertion, as I was the only trainee in data management department. Nevertheless, this task helped me developing some skills like accurate and faster typing. But the most important benefit was the fact that it helped me design friendlier databases. If a database developer does not have considerable experience in data entry, he/she might create database that are not efficient from a data entry point of view. This, together with my scientific background, allowed me to create well designed and user-friendly data bases. In the end, it was an experience that I did not enjoy while I was doing it, but now I recognize that it was quite useful for my professional future in data management.

My biggest difficulty in this department was the creation of databases in Microsoft Access© because I had only basic knowledge from high school. However, I had specific training in Keypoint, which I complemented with autonomous study, so I quickly became independent on the development of databases in this software. Another big challenge was

the creation of a database and posterior data entry of an observation study in Spanish. Since it is already hard to understand the doctors' handwriting in Portuguese, in Spanish it was even harder. However, my background in biomedicine proved again to be an asset for this task.

Actually, my main advantage in this department was the fact that I was the only element of the staff with scientific and clinical research background, which proved to be very useful. Thanks to this, I was able to understand better the free text fields in the CRFs and to detect aberrant values in the clinical or laboratory variables. Also, the soft skills like autonomy and curiosity developed during the MSc were essential to facilitate my learning and independent work.

Since it is not possible to cover all these data management tasks in the MSc classes, as they are quite practical, time consuming and require face-to-face support systematically, this experience in Keypoint was essential to complete my theoretical education from the MSc. In fact, this experience proved to be essential to continue my career in data management.

I can say that I help creating important tools for the company as, when I left, there were still several studies on-going with databases developed by me.

3.4. Statistics

In the statistics department, I had the chance to be involved in very diverse study reports from simple observational studies to very complex clinical trials, across a wide range of therapeutical areas. Also, some studies were investigator-sponsored studies while others were sponsored by the pharmaceutical industry. All of these reports provided me a vast experience in statistics and significantly furthered my knowledge in this area. It is worthy to point out that, from statistical point of view, it is quite different to analyse a clinical trial and an observational study. The number and complexity of the variables was remarkable in clinical trial. Also, in a clinical trial usually there are much more subjects enrolled so it was easier to apply parametric tests instead of non-parametric, like it was usually necessary in observational studies. It should also be pointed that among the industry sponsored studies that I dealt with, were both clinical trials and observational studies, while all the investigator sponsored studies were observational studies.

However, my favourite task in the statistics department was the Euro 2012 study. This was study for a thesis of a PhD student which aimed to analyse the relationship between the strategy (e.g., number of passes, zone of passes, zone of shoots, number of shoots, etc.) of the football teams that participated in Euro 2012 with the position of those teams in the tournament. I especially enjoyed this study because it was completely different from all the other studies that I was involved and it had a theme that I found personally interesting. Since it was not a clinical study, I had to think in a different way because we it is not possible to use the same type of thinking for these type of study. Also, I had to use different statistical tests that I did not have the chance to use for the clinical trials or observational studies.

I would not say I had a task that I liked the least since I also enjoyed all the other studies which I was involved in.

I had some difficulties in the statistic department because, despite I had had two statistics subjects in the MSc and I had a good theoretical knowledge, I was lacking the practical experience to make statistical analysis for the most complex studies. Because of this, in the beginning of the internship, I felt unprepared to cooperate in this area. However, I had necessary knowledge and motivation to learn on the job and, by the end of the internship, I felt that I had significantly furthered my knowledge in statistics.

4. Conclusion

This internship was a great experience because I grew not only as a professional but also as a person. I furthered my knowledge in both data management and statistics areas and I had the change to apply what I learned in the MSc in real life scenarios. I improved my soft skills like communication, improvisation, time-management, prioritization, team work and autonomous work. However, I cannot say that I was able to fulfil all my internship objectives. Despite I learned a lot in statistics, I still do not feel fully capable to work independently in this field.

Keypoint was a great place to start my professional career. The fact that it is a small CRO, I had the chance to be involved in almost all projects and not only with all members of staff of Data Management and Statistics but also from the other departments. Also, the familiar environment of the company allowed me to be more relaxed and feel more part of the team. I also felt that I became a value member in the company and I believe that I have left my mark there.

By having an internship in two core areas, it helped me define my future career. Despite my initial preference for statistics, I found out that I am still not ready to independently work in this area and I, actually, I don't enjoy it as much as I thought. On the other hand, I learned to enjoy data management and I believe my future will pass by on this area.

It is undisputable that the Masters was fundamental to the success of my internship. The multidisciplinary education focused not only on the present, but also in the future of clinical research, gave the knowledge to be a useful member in Keypoint very quickly. The Problem-Based Learning (PBL) of the Bachelor's Degree in Biomedical Sciences of University of Aveiro was also invaluable to this success. The fact that I was able to learn most of the things by myself after just a brief training quickly made me a valuable asset for Keypoint. Also, the extracurricular projects like the internship in Hospital Infante D. Pedro (HIP) and my cooperation with the Gabinete de Investigação Clínica da Universidade de Aveiro (GIC) made the transition between the university and work realities easier.

In the future, I hope I can continue to improve my knowledge and skills in data management while collaborating in the expansion of the reputation of Masters in Pharmaceutical Medicine.

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