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Domingues Costa
Marques**

**RELATÓRIO DE ESTÁGIO CURRICULAR NA
W4RESEARCH – CONTRACT RESEARCH
ORGANIZATION**

**CURRICULAR TRAINING REPORT AT
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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 orientação científica da Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada do Departamento de Ciências Médicas da Universidade de Aveiro e do Mestre Pedro Miguel Rafael Barbosa da Rocha, Diretor de Recursos Humanos e de *External Affairs* da W4Research, Lda.

Curricular training report to be presented to the Aveiro University to fulfil the necessary requirements for the Master's Degree in Pharmaceutical Biomedicine, held under the scientific guidance of Maria Teresa Ferreira Herdeiro, Assistant Professor, Department of Medical Sciences, University of Aveiro and Pedro Rocha, Human resources and External Affairs Manager at W4Research, Lda.

Dedico este trabalho à minha família, namorada e amigos, pelo incansável apoio prestado e pelos momentos de alegria que me proporcionaram, durante esta jornada.

o júri

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agradecimentos

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palavras-chave

W4Research, CRO Full Service, CRA, Investigação Clínica, Estudo Observacional, Medical Writing e Boas Práticas Clínicas

resumo

O presente relatório destina-se a descrever as atividades desenvolvidas no âmbito do estágio curricular que teve lugar na W4Research, uma *Contract Research Organization* (CRO). O estágio teve a duração de 8 meses durante os quais o estagiário desempenhou funções de CRA sendo o principal foco a monitorização de estudos observacionais. Para além da principal atividade, foram ainda desenvolvidas funções em áreas adjacentes à investigação clínica, tais como, o *Medical Writing* e a gestão da qualidade.

Este trabalho pretende mostrar a visão obtida e os pontos de vista do estagiário enquanto monitor de estudos observacionais.

keywords

W4Research, CRO Full Service, CRA, Clinical Research, Observational Study, Medical Writing and Good Clinical Practices.

abstract

This report intends to describe the activities carried out under the traineeship which took place in W4Research, a Contract Research Organization (CRO). The internship had the duration of 8 months during which the trainee worked as a CRA, being the main focus the monitoring of observational studies. Besides the main activity, the trainee also had the opportunity to perform adjacent functions to the clinical research, such as Medical Writing and quality management areas.

This document intends to show the obtained vision and the points of view of the trainee while monitoring observational studies.

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ABBREVIATIONS

AB	Administration Board
AE	Adverse Event
APIFARMA	<i>Associação Portuguesa da Indústria Farmacêutica</i> (Pharmaceutical Industry Portuguese Association)
CEIC	<i>Comissão de Ética para a Investigação Clínica</i> (Portuguese Ethics Committee for Clinical Research)
CNPD	<i>Comissão Nacional de Protecção de Dados</i> (Data Protection National Committee)
COV	Close-Out Visits
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trial
eCRF	Electronic Case Report Form
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
FDA	Food & Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
INFARMED	<i>Autoridade Nacional do Medicamento e Produtos de Saúde</i> (National Authority of Medicines and Health Products)
ISF	Investigator Site File
ISO	International Organization for Standardization
MA	Marketing Authorisation
MAHs	Marketing-authorisation holders
MW	Medical Writing
NME	New Molecular Entity

OS Observational Study
PD Pharmacodynamics
PI Principal Investigator
PK Pharmacokinetics
PAES Post-authorization efficacy studies
PASS Post-authorization safety studies
PRAC Pharmacovigilance Risk Assessment Committee
QMS Quality Management System
SAE Serious Adverse Events
SD Service Director
SDV Source Data Verification
SIV Site Initiation Visit
SMV Site Monitoring Visit
SOP Standard Operating Procedure

1. INTRODUCTION

In the scope of the second year of the Master's degree in Pharmaceutical Biomedicine, I applied and went through an internship at W4Research, a full service contract research organization (CRO) placed in Lisbon, that had a duration of 8 months.

This internship came in the sequence of one year receiving theoretical training in a wide set of matters related with the clinical research, particularly the drug life cycle, which includes clinical studies, monitoring, regulatory activities and pharmacovigilance. Although it was the monitoring activity, which arouse me more interest, my aim was to carry out an internship covering practical experience in several areas within clinical research. I wanted my internship was not be too focused in one area. The chance to perform internship at W4Research interested me, because this is a new and small company, it could allow me to perform tasks in various areas.

Thus, from November 2015 to June 2016 it was developed the "on job training" where the main focus was observational study monitoring along with several working areas linked to clinical research, described in this report. The internship consisted of two different strands of work: the on- site monitoring and the remote monitoring along with other office based activities.

The leading aim of this training report is to describe my experience at W4Research, In order to evaluate and appraise the performance during the training, it was settled the following learning outcomes to be accomplished during the internship:

Primary objectives:

- To consolidate and be able to apply the theoretical knowledge assimilated during the Master's degree;
- To get experience on the field of clinical research with expertise to clinical studies monitoring alongside with all the particular intrinsic skills of conducting a clinical study;
- To obtain professional experience by integrating a clinical operations team inside the company which will allow to acquire soft skills that are needed to go further on the work market;

Secondary objectives:

- To go through the company functional dynamics and understand the business model of pharmaceutical industry;

- To improve the management of interpersonal skills and to strengthen team building and team working skills

This report is organized in several chapters chained in a logical manner to ease the access of all:

- **Chapter 1**, the introduction, is presented the context and the motivation of this report as well as a brief note about the host institution; it is described the objectives and the structure of the document;
- **Chapter 2**, the State of the art, in this chapter the activities that were developed during the internship are describe and they are divided into two sections, one concerning the specific monitoring training and other related to other clinical research related activities;
- **Chapter 3**, On-the-job-monitoring, are described the activities performed during the internship. These activities are separated from the specific training on clinical monitoring and the generic training which contains activities in different areas;
- **Chapter 4** covers some formation I received during my internship;
- **Chapter 5**, the discussion, are evaluated the competences and know-how acquired during the internship;
- **Chapter 6** covers the conclusions about this training report.

1.2 HOST COMPANY OVERVIEW

My host institution, W4Research Lda. - "Work for Research" - is a full service CRO with capital 100% Portuguese, established in April 2014. It is a scientific and marketing consultancy organization, working in health area. Constituted by a multidisciplinary team, with recognized experience in consulting, health research and training, acquired in Pharmaceutical Industry and Contract Research Organizations environment.

W4Research, hereinafter referred to as W4R, combines expertise in health research, medicine, marketing and social sciences.

The slogan "Working for science, health and the future," leads to the W4R's mission, which is the production of clinical and scientific knowledge through collaboration with institutions and companies, providing the following services:

- Consulting – Providing all the services necessary for the clinical development of new drugs, including the implementation of Phase I to Phase IV clinical trials

and observational studies (OS), as well as socio-epidemiological and registry studies. Providing services such as, study development (study design, protocol, informed consent form, case report forms (CRF)), clinical monitoring (feasibilities, submissions, monitoring, pharmacovigilance), data management (eCRF, databases development, data-entry, queries), statistics, medical writing (clinical reports, articles, posters), but also advisory boards, regulatory affairs, audits and quality control.

- Training – This service includes training options in clinical research, but also in complementary areas such as behavioural training, medical writing, time management, communication and conflict management, among others.
- Resourcing – The focus of W4R for this service is in the human resources. With the ability to help in the recruitment and development of new collaborators, and / or allocation of specialized human resources to customer service.(1)

W4R provides services in national and international markets proposing to become a reference in this market, based on excellence standards, and permanent updating of scientific and regulatory knowledge, bearing in mind the sustainability of the organisation and professional development of collaborators. Focus on client is the main concern of W4R, in order to create value. W4R identifies as potential clients: pharmaceutical industry, medical societies, hospitals, investigators, biotechnology industry, study groups, other CROs.

The organization chart is represented in Figure 1.

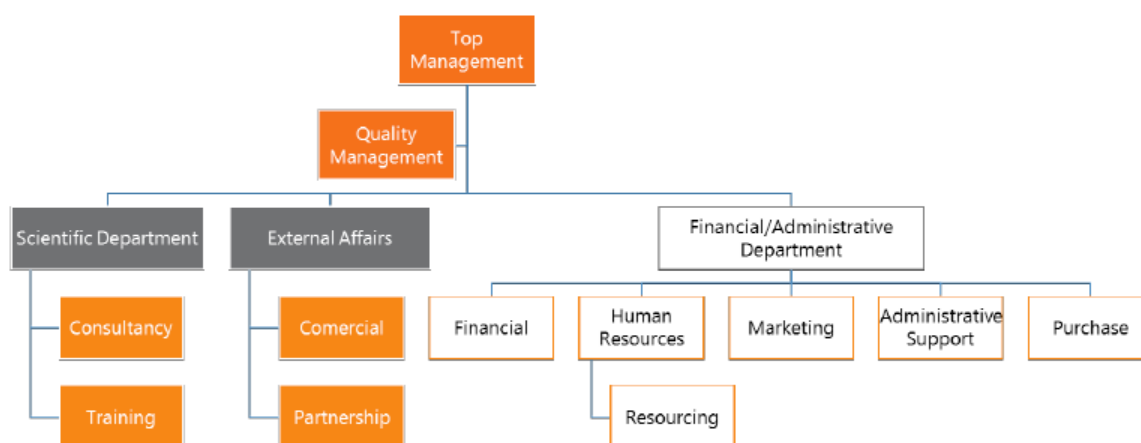


Figure 1. W4Research organization chart.

The top management leads the hierarchy, in close collaboration with the quality management, in order that their decisions allow to maintain the standards of excellence in

the services provided. In the scientific department is the team that provides the consulting and training services. External affairs comprise the commercial and partnership departments. Are part of financial and administrative department: finance, human resources, marketing, administrative and purchases. Within the human resources department is included the resourcing service.(2)

2. STATE OF THE ART

My background formation gave me knowledge in health and clinical research areas that would reveal to be useful during my internship in W4R. There are concepts and processes, which serve as starting point for the exploration of this broad area of research. In this section I introduce the points that most relate to the activities carried out in my internship, which are: the drug life, contract research organizations, OSs, the state of the art of clinical research in Portugal and the regulatory framework as well as, entities involved in this process.

2.1 DRUG LIFE-CYCLE

The life cycle of a product, integrates basic research of new molecule that will lead to a new therapy, followed by clinical research whose major objective test new therapeutic compounds developed confirming the findings and tests in the laboratory. In this chapter I will briefly describe all the phases that compose this cycle, giving more attention to clinical research, once it is my main training area.

2.1.1 DISCOVERY

The first step to find a new molecular entity (NME), that may will originate in the future a new drug, is identify a biological target, which is any structure or molecule, such as a nucleic acid or a protein, within a living organism which is intended to be matched by some other entity.

The investigators should make a target validation, setting whether the target can be influenced by a new drug, and consequently identifying the most promising approach. This analysis must happen before developing thousands or even millions of molecules which will be undergo a screening procedure, increasing the efficiency and effectiveness of the R&D process.

A lead compound is a chemical compound that has a pharmacological or biological activity likely to be therapeutically useful.

To produce a therapeutic effect is need induce an interaction between a lead compound and a biological target. Once identified a potential lead compound, this goes through an optimization and validation process, to provide preliminary assessment of safety and efficacy profile of the future drug which can come from this new entity.

A process of patent application is then followed, thereby granting to the inventors the exclusive right with respect to their potential new drug developed from this molecule or biological entity, without others being able to copy and sell it for a set period of time.(3)

2.1.2 PRE-CLINICAL STUDIES

After the patent is conceded, the new drug advances to the pre-clinical tests stage where preclinical safety and pharmacology are assessed. These studies are developed both in vitro and in vivo models. At this phase the in vivo models are mammals such as rodents, dogs or monkeys. The species selection is done according to the intended end of the research and which of the species, at the light of the latest knowledge is believed that can more precisely simulate the drug action inside the human organism. The principal objective of the preclinical development of a compound is to assess its safety profile. The nonclinical safety assessment usually includes pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that are cause for concern are intended for a long period of use, an assessment of the carcinogenic potential. Considering the size of the population at risk and the less controlled conditions in clinical practice, may be extremely important to extend the duration of non-clinical tests.(4)

2.1.3 CLINICAL DEVELOPMENT

The next step in the development process of a new drug are the Clinical Trials (CT), in order to demonstrate the safety and efficacy, before receiving the Marketing Authorisation (MA).

The history of CT as a concept is relatively recent. Biblical excerpts, dating back to 500 BC, describe investigations that can be considered as proto CTs. However, the first record of something similar to CT, occurred in 1747 when a British physician named James Lind, conducted the first, controlled clinical investigation, whilst working as a surgeon on a ship, and observed a high mortality by scurvy, amongst the sailors. Dr. James Lind selected twelve sailors diagnosed with scurvy, with the same symptomatology, in order to identify the most promising treatment for this disease. He divided them into 6 groups giving different therapeutic each, and concluded that the group that received treatment of citrus, had better results.(5,6)

In early of 20th century, clinical trials began to be heavily regulated, when government authorities recognized the needed to control medical therapies. ICH-GCP, defines CT as, "any investigation in human subjects intended to discover or verify the clinical, pharmacology and/or other pharmacodynamics (PD) effects of an Investigational Medicinal Product (IMP), and/or to identify any adverse event (AE) to an IMP, and/or to study absorption, distribution, metabolism, and excretion of an IMP with the object of ascertaining its safety and/or efficacy". Another definition of CTs which supports the ICH-

GCP definition is describe in No. Law 21/2014 of 16 April. In which the clinical studies with intervention, such as the CTs, are any research that supported a change, influence or programming of health care, behaviour or knowledge of the participants or caregivers, in order to discover or verify effects on health, including exposure to drugs, use of medical devices, implementing surgical techniques, exposure to radiation, the application of cosmetics and personal hygiene, physiotherapy and/or psychotherapy interventions, the use of transfusion, cell therapy, participation in individual education sessions or group intervention with diet, to intervene in access or organization of health care or the intervention referred to as unconventional therapy.(7)

CTs can be classified according to a temporal classification of the phases (from phase I to IV) or according with the objective: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use. Both classifications can be related to each other having some kind of transposition therefore, since one type of trial may occur in different temporal phases (please see figure 2). Based on this, it is preferable to use the classification system based on the own objectives.(8)

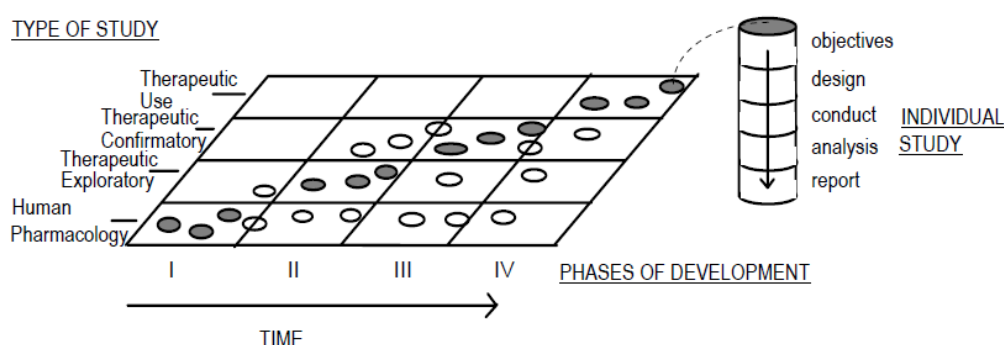


Figure 2. Correlation between development phases and types of clinical studies. Adapted from (8).

The different phases of CTs can be described as follows:

- Human pharmacology (phase I) studies, usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or restricted groups of patients (e.g. drugs with significant potential toxicity). These first-in-human trials of a new potential drug have the objectives of assess safety and tolerance, describe the pharmacokinetics (PK) featuring drug's absorption, distribution, metabolism, and excretion (ADME) as well as PD profiles of the drug, exploring the drug metabolism and interactions, and estimating the activity of the drug. Some examples of these studies are dose-tolerance studies, single and multiple dose PK and/or PD studies and drug interaction

studies. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations;

- Therapeutic exploratory (Phase II) studies, are normally conducted in reduced groups of patients, who are selected by relatively narrow criteria, representing a homogeneous population. Its primary objective is to explore the therapeutic efficacy in subjects with the intended disease to treat. These studies are aimed to explore the use of the drug for the targeted indication, to estimate the dosage for the subsequent studies and to provide the basis for confirmatory study design, endpoints and methodologies. Therapeutic exploratory CTs may use a variety of study designs, including concurrent controls and comparisons with baseline status. Some other study examples are earliest trials of relatively short duration, using surrogate or pharmacological endpoints or clinical measures and dose-response exploration studies;
- Therapeutic confirmatory (Phase III) studies, has as primary endpoints to demonstrate or confirm efficacy of the drug, to establish a safety profile, to provide an adequate basis for assessing the benefit/risk relationship to support licensing and to explore the dose-response relationship. These trials involve wider populations, are adequate, and well controlled in order to establish efficacy. Randomized parallel dose-response studies, clinical safety studies, studies of mortality/morbidity outcomes, large sample trials and comparative studies, comprise the variety of studies of this stage of clinical development;
- Therapeutic use studies (Phase IV) are all the studies conducted after MA and related to the approved indication. These studies have as objectives, refine the understanding of the benefit/risk relationship in general or special populations and/or environments, identify the less common AEs and revise the dosing recommendation. Examples of studies are comparative effectiveness studies, drug-drug interaction, studies of mortality/morbidity outcomes, studies of additional endpoints, large simple trials and pharmacoeconomic studies.

2.1.4 AFTER COMMERCIALIZATION

After proving its efficacy and safety, new potential entities can be proposed for a MA, and if approved can enter the market. However, research on a new medicine does not end when the discovery and development phases are completed and the medicine is available to patients. Pharmacovigilance, defined by WHO as "the science and activities Relating to the detection, assessment, understanding and prevention of adverse effects or

any other medicine-related problem", is the process that follows in the new drug cycle, after being commercialized. Furthermore, companies conduct extensive post-approval studies to monitor safety, long-term side effects and efficacy, and may also pursue research into new indications for the medicine in different disease areas, age groups, or other patient populations.(9,10)

At this point there are, among others, the Post-authorization safety studies (PASS) and Post-authorization efficacy studies (PAES).

- Post-authorization safety studies

PASS is defined by European Medicines Agency (EMA) as "Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk minimisation measures."(11)

The data collected from the PASS aims to: identify, characterise or quantify a safety hazard; confirm the safety profile of a medicine; and/or measure the effectiveness of risk-management measures. PASSs can be voluntary, when they are conducted by Marketing-authorisation holders (MAHs), on their own initiative, for example to fulfil risk-management plan demands. On the other hand, PASSs can be imposed by a competent authority, in order to grant the marketing authorization, or; after the marketing authorisation if there are concerns about the risks of the authorised medicinal product. If they are imposed, the entity responsible for evaluating the protocols and subsequently the results, is the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). The MAH has the responsibility to ensure that the PASS is not a clinical trial. (12)

- Post-authorization efficacy studies

PAES is a study conducted within the authorized therapeutic indication to complement available efficacy data. These studies take into consideration well-reasoned scientific uncertainties on the evidence of benefits that could not be resolved prior to authorization or where identified after authorization.

PAES may be initiated by a MAH voluntarily, or pursuant to an obligation imposed by a competent authority. In the past, PAES were typically only required for medicines approved conditionally or under exceptional circumstances.

In the scope of Commission Delegated Regulation (EU) No 357/2014, national regulatory authorities, EMA or the EC can require PAES:

"Where concerns relating to some aspects of efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed;

Or

where the understanding of the disease, the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly."(13,14)

The following situations may be considered possible PAES scenarios: studies aimed at determining clinical outcome following initial assessment based on surrogate endpoints; studies on combinations with other medicinal products; studies linked to a change in the understanding of the standard of care for the disease and/or the pharmacology of the medicinal product; studies aimed at determining the long-term efficacy of a medicinal product and; studies in everyday medical practice, like observational studies or pragmatic controlled trials.(15)

2.1.5 NEW PARADIGM IN R&D

The pharmaceutical industry has had substantial losses in revenue, once the traditional drug R&D process is going through a productivity crisis. The expiration of patents, the increasing demands of regulatory requirements and complexity of the protocols. The R&D process for new drugs is costly (1 Billion € approximately) and very time consuming (10 - 15 years), and it ends more often in failure than in success - less than 12% of drugs that come into trials clinical get approval. These are the main bottlenecks to drugs R&D productivity. Furthermore, this development model does not provide strong evidence to support early "go/no-go" decisions.

For all these, it is globally recognized that the traditional pathway for drug R&D, is depleting resources and halting the discovery and development of new therapies. Therefore, must be adopted a new faster, cheaper and dynamic approach.(3,16)

However, not everything is negative, the consistent evolution that basic science has performed in what concerns to the "omics" technologies, imaging techniques, sophisticated computational methods and powerful types of biomarkers, are significant achievements.(17)

The big issue lies in the faulty transition of knowledge from basic science to application in the development of new drugs. Representing a large gap of translational research, defined as the translation of research into better health, encompassing a dynamic and continuous cycle, where new knowledge is being generated, moving in a bidirectional continuum: from researcher's bench to the patient bedside and back again.(18,19) To overcome this gap have been suggested in recent years, several approaches aimed to

improve the translational process between basic and applied science, in particular, the transition from preclinical to clinical development. One of such approaches is the "Quick win, fast fail" model, published by Steven M. Paul et al in 2010(16). The comparison between the traditional and the proposed approach is shown in Figure 3.

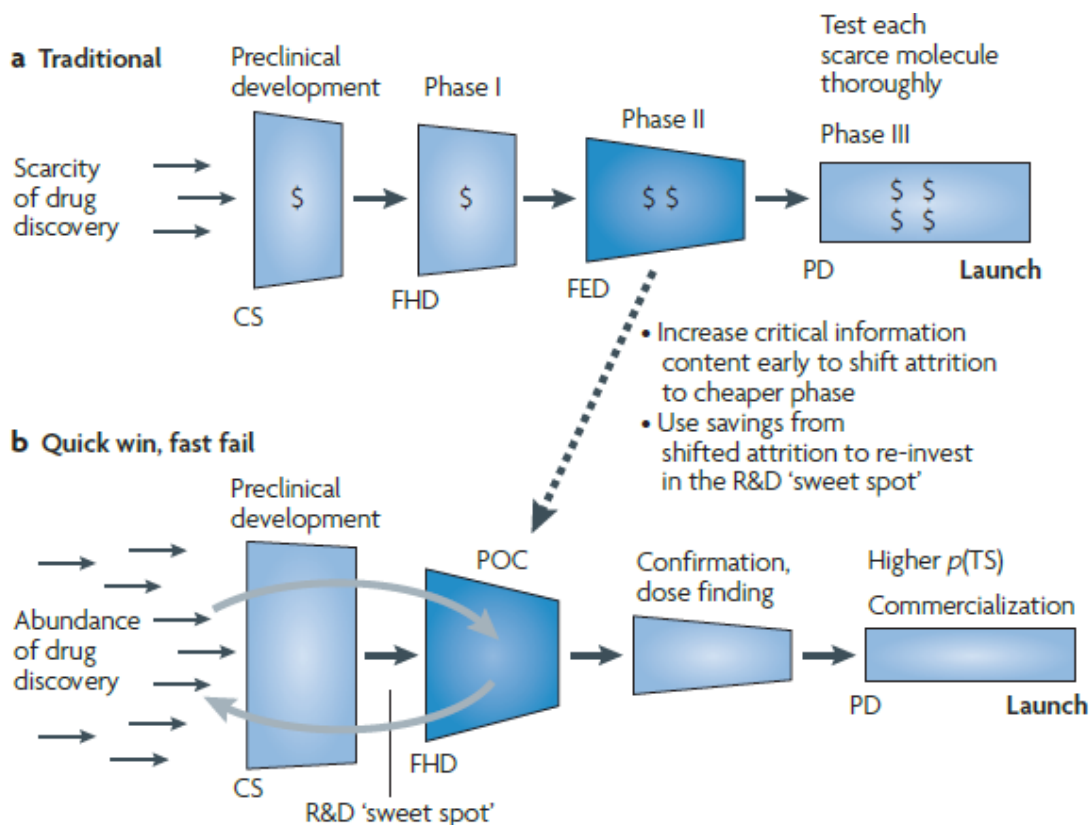


Figure 3. The “quick win, fast fail” paradigm. This figure compares the traditional paradigm of drug development (a) with the "quick win, fast fail" drug development paradigm (b). This alternative paradigm, reduces uncertainty through the earlier achievement of PoC, advancing to the costly confirmatory phases (Phases II & III), in order to obtain MA, only the drug candidates that have a higher probability of success. CS – Confidence in Safety, FHD – First Human Dose, FED – First Efficacy Dose, PoC – Proof-of-Concept, PD – Product decision. Adapted from (16).

This model aims to improve the predictive value of preclinical and clinical studies, using the recent developments of basic science, mentioned above, such as genomics, proteomics and bioinformatics. New molecular targets have been discovered, through the increasing knowledge about the molecular pathology of the disease, leading to abundance in drug discovery. According to this model, to convert this knowledge into new drugs, more safe and efficient, it is necessary that PoC is achieved sooner, preferably in phase I, so that, more drug candidates could be tested earlier, in less costly phases.

This approach is based on a constant shift between the pre-clinical and early development phase (phase I), called "sweet spot" of R&D, where the candidate drugs are tested for PoC until a candidate proves that it is a safe investment to advance to expensive confirmatory phases.(16)

Another alternative approach to drugs R&D process, is described in the PWC's report: "Pharma 2020: The vision", from 2008. In this approach are introduced the concepts of "live license" and "in-life testing". According to the report, in 2020, the new drugs will receive a MA in real time - live license - which will be dependent on the performance analysis of new data collected through the drug commercialization - in-live testing.

These principles should be based on solid and constant communication and sharing of information between pharmaceutical industries and the regulatory authorities. Thus, if the evidences from "in-live testing" that the new drug is safe and effective is obtained, through the in-live testing, new therapeutic indications are added to the previous license, and consequently extending the MA to other segments of the population, as presented in Figure 4.(17)

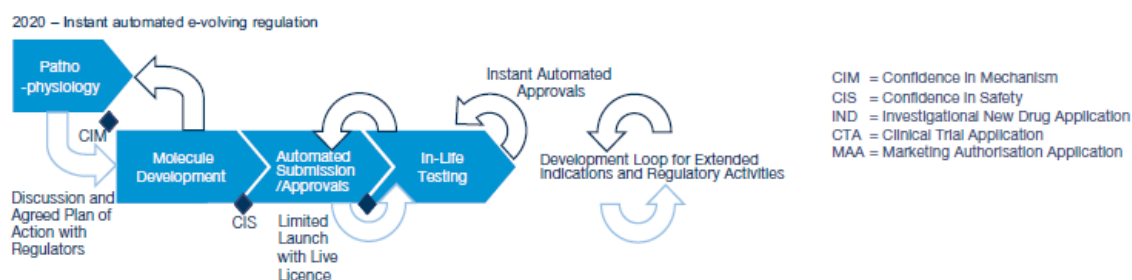


Figure 4. The concepts of “live license” and “in-life testing”. Adapted from (17).

The "real world evidence" is increasingly important to the R&D process of new drugs. These data can be collected through observation of clinical practice (OS) as well as, with studies during Phase IV clinical study. These data are named "real world data" because are collected from real people, contrary to a controlled environment. These data once collected, should be analysed and processed, generating the "real world evidence". These evidences will support new studies, new drugs, new indications, and therefore will support the "live license and in-live testing" model.(17)

2.1.6 OBSERVATIONAL STUDIES

OS also called epidemiological studies are those in which the investigator is not acting on the study participants, ie without the recruitment of patients in a controlled

environment, but instead observing natural relationships between factors and outcomes.(20)

According to Portuguese Law 21/2014 of 16th of April, OSs must fulfil the following conditions:

- The drugs are prescribed or medical devices are used in accordance with the conditions of AIM or conformity assessment procedure, respectively;
- The inclusion of the participant in a particular therapeutic strategy is not decided in advance by a trial protocol but depends on the current practice;
- The decision to prescribe the medication or use a medical device is clearly separated from the decision to include or not the participant in the study;
- Do not be applied to the participants any additional diagnostic procedure or evaluation and epidemiological methods are used to analyse the collected data.(7)

OSs are defined by the type of methodology and not by the scientific objectives, and may be classified in different ways, depending on how the groups are compared and the time period. In this context, a study can be retrospective if the research is limited to the past or prospective, if data collection is done after the patient give his consent.

Thus, with respect to OSs, and specifically to analytical OSs, we must consider the following study designs:

Transversal

- Cross-sectional studies, are used to evaluate a sample, representative of the population, on a single point of time, so it is described as a "snapshot". Cross-sectional studies are typically retrospective, wherein the sample is selected only based on exposure status. Outcomes status is obtained after participants are enrolled. One of the main measures of this type of study is the prevalence, so it can be used to calculate the prevalence of a disease in a given geographical location. Cross-sectional studies are also suitable to study a hypothesis, since they require less resources, less time and allows the study of a diversified population stratum. The sample randomization is very important in this type of observational study, since a selection bias may result in imperfect measure of the prevalence and risk for the exposure-outcome relationship calculation.(21)

Longitudinal

- Cohort Study, provide data for a specific population, over time. Such studies can be either retrospective (using information already available records in file) or prospective (following a specific group of individuals, for a specific period of time). Cohort studies start with exposed individuals and not exposed to a factor in order to assess the evolution and outcome. These factors can be identified by cross-sectional studies and then followed in cohort studies. The cohort studies are appropriate when:
 - There is an association between exposure and outcome, proven by strong evidences (e.g.: by a previous cross-sectional study);
 - The time period between the exposure to the factor and development of outcomes is short in order to minimize losses to follow-up;
 - The outcomes are not very rare.

Cohort studies are used to determine the incidence and / or observe the evolution of a standard treatment of a disease.

- Case-control studies, are implemented when seeking to establish an association between exposure and a certain outcome. Thus, individuals who present the outcome are called "cases" and individuals on the contrary do not show the outcome are the "controls". These two groups are compared in what regards their past exposure to the factor being studied. This type of studies are typically retrospectives, and instead of cohort studies these are appropriate to study rare diseases or conditions, requiring that there is evidence of exposure to study factor in the past. Recall bias is an important issue when you are determining past exposure. Since this is usually determined through interviews with individuals or analysis of historical records. And if cases and controls recall past exposures differentially, or if the level of information in the records is not the same for both groups, the study results may be biased.(20)

Regarding the descriptive OSs, we must consider the following design:

Ecological Studies

In addition to the analytic OSs presented above, there are also descriptive OSs, and ecological studies stand out in this category. In ecological studies the unit of observation is the population or community. Disease rates and exposures are measured in each of a series of populations and their relation is examined.

These two OSs approaches (analytical and ecological) differ primarily in the supportive evidence they can provide about a possible causal association. Unlike the analytical study, an ecological study does not link individual outcome events to individual exposure or confounding characteristics, and it does not link individual exposure and confounding characteristics to one another.(22)

An example of an approach to an ecological study, it may be the study of a migrant population. The study of migrant populations offers a way of discriminating genetic from environmental causes of geographical variation in disease, and may also indicate the age at which an environmental cause exerts its effect. Second generation Japanese migrants to the USA have substantially lower rates of stomach cancer than Japanese people in Japan, indicating that the high incidence of the disease in Japan is environmental in origin. In first generation migrant's rates are intermediate, which suggests that the adverse environmental influences act, at least in part, early in life.(23)

2.3 CLINICAL RESEARCH ENTITIES

The area of clinical research is widely regulated, worldwide, with transpositions and particularities to each country. In order to better understanding of this regulatory environment, following a brief description of some institutions involved in this regulation:

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is the unique combined initiative between regulatory authorities and the pharmaceutical industry from United States, Europe and Japan. Its goal is to discuss scientific and technical aspects of drug registration. By harmonizing the regulatory processes and obligations it ensures that safety, effectiveness, and high quality standards are applied in new medicines development and that its registering is carried in the most resource-efficient manner;(24)
- European Medicines Agency (EMA) is the regulatory agency of the European Union (EU), located in London. It is responsible for protecting and promoting public and animal health, 28 Member States of the EU and the countries of the European Economic Area, running a scientific evaluation, surveillance and monitoring of drug safety for human and veterinary use developed by pharmaceutical companies for use in the EU. The EMA has seven scientific committees to carry out their scientific evaluation. In addition, the agency has a number of working parties and related groups, which the committees may consult on scientific issues related to their specific area of expertise;

- EMA also monitors the safety of medicines by the establishment of a wide Pharmacovigilance network and stimulates the continuous research improvement in pharmaceutical area;(25)
- INFARMED is a public institute included in the indirect administration of the State. This signifies that INFARMED is endowed with administrative and financial autonomy and has its own patrimony. INFARMED IP is a central body with jurisdiction over the entire Portuguese territory and acts by regulating and supervising the areas of drugs, medical devices, cosmetics and personal hygiene products according with the highest standards. Its mission is to protect public health and ensure access to health professionals and citizens to medicines, medical devices, cosmetics and personal hygiene products with quality, effectiveness and safety;(26)
- Comissão Nacional de Proteção de Dados (Data Protection National Committee) (CNPD) is an independent administrative body with powers of authority. Generally, has the function to control and monitor the processing of personal data, in strict respect for human rights and fundamental freedoms and guarantees in the Constitution and the law. In addition to being the national authority of personal data control, has also attributed the actions of research and inquiry, intervention in legal proceedings and to caution or censure publicly responsible for processing the data. The CNPD cooperate with the data protection supervisory authorities of other states, particularly in the defence of people living abroad and in the exercise of their rights;(27)
- Associação Portuguesa da Indústria Farmacêutica (APIFARMA), founded in 1975, represents more than 120 companies responsible for Production and Import of Medicinal Products for Human and Veterinary Use, Vaccines, and In Vitro Diagnostics. It aims at solving common problems, the socio-economic development of the sector and the country, the improvement of health in Portugal and greater patient access to new therapies;(28)
- International Organization for Standardization (ISO) is an independent, non-governmental organization made up of representatives from national standards bodies of 163 countries. Its aim is to help simplify the coordination and unification of international industry standards, through its members, which bring together experts in order to share knowledge and develop voluntary international standards that support innovation and prepare industry for future challenges;(29)

- Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services and is responsible for promoting public and animal health. To this end, FDA regulates and monitors food safety including supplements and food additives, tobacco products, biological products, pharmaceuticals, medical devices, veterinary products, cosmetics, etc;(30)
- Comissão de Ética para a Investigação Clínica (National Ethics Committee for Clinical Research) (CEIC) is, according to the provisions of Law No. 21/2014 of 16 April, "the independent body consisting of healthcare professionals and others responsible for ensuring rights protection, safety and well-being of participants in clinical trials and to ensure the same with the society. " In order to comply this goal, the CEIC carry out an evaluation of protocols related to clinical trials and/or studies with the use of medical devices for human use submitted to it, and then sends an ethical opinion on these studies.(31)

2.4 REGULATORY FRAMEWORK

Behind the practice of clinical research there is a general set of regulatory documents that serve as guidelines, representing a working basis for all professionals in this area. These guidelines have information pertaining to research procedures, covering medical aspects and ethical considerations.

2.4.1 WORLDWIDE DOCUMENTS

- In 1947 the Nuremberg Code was elaborated in answer to the atrocities committed during World War II, especially the medical experiments conducted in concentration camps by the Nazis where prisoners were tested without any kind of agreement. These experiments led to deaths and disabilities in thousands of human beings. The principal aspect of the Nuremberg Code is the demanding that all CTs performed in a person must have his informed consent form (ICF);(32)
- The Helsinki Declaration appeared in 1964 in answer to the Thalidomide disaster in which thousands of babies born with abnormalities due to lack of knowledge about secondary effects in pregnant women when taking that drug. This declaration specifies a series of ethical principles for medical research involving human subjects and must be follow in all clinical researches. It suffered 10 amendments seven times since 1964, with the last one having occurred in 2013, adopted at World Medical Association (WMA) general assembly;(33)

- The ICH-GCP E6 is a document which final version was issued in May 1996 and intends to standardize clinical research in all three ICH regions: United States of America, Europe, and Japan. Responsibilities and expectations of each participant of a CT, specifically the sponsor, the investigator, monitor, IRBs and the CT coordinator amongst many others are described in this document;(34)
- Guidelines for Good Pharmacoepidemiology Practice (GPP), it was first published in 1996, and its last revision is dated June 2015. It proposes practices and procedures aiming to help ensure the quality and integrity of pharmacoepidemiological research and provide adequate documentation of research methods, encouraging the collection of accurate data, consistent analysis and construction of robust reporting;(35)
- Guidance on Good Pharmacovigilance Practices (GVP), represent a set of measures designed to help the pharmacovigilance process in EU countries. This guideline is applicable to MA holders, to own EMA, and each member state drug authorities. They are divided into two broad categories, the various pharmacovigilance processes and specific considerations for products or populations. The GVP also helps in the planning and implementation of risk minimization measures in order to prevent or reduce the occurrence of AEs associated with drug exposure.(36)

2.4.2 EUROPEAN LEGISLATION AND PORTUGUESE TRANSPOSITIONS

- Law No. 21/2014 of 16 April, also called "law of clinical research." This law covers the transposition of Directive 2001/20 / EC of the European Parliament and of the Council of 4 April on the approximation of the laws of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use and also the clinical research system of medical devices arising from the partial transposition of Directive 2007/47/EC. (7,37) This new law has undergone a change described in Law No. 73/2015, of 27 July;(38)
- Law No. 67/98 of 26 October, "Personal Data Protection", which stems from the transposition of the 95/46 / EC directive, the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data;(39,40)

- Deliberation No. 1704 / 2015 apply to personal data processing carried out in the framework of Clinical Investigation. This deliberation lays down the guiding principles of the processing of personal data of participants in clinical research, in the light of Law No. 67/98 of 26 October, as well as the Law of Clinical Research and Decree-Law No. 145/2009 of June 17, repealing the deliberations No. 227/2007 of 28 May 2007 and No. 333/2007 of 16 July;(41)

For implementing a clinical trial in Portugal is mandatory to obtain approval from the INFARMED I.P. and from the CNPD. Is also mandatory to obtain a favourable opinion from the CEIC. Furthermore, the study centre Administration Board (AB) must authorize the study and may require the favourable opinion from the local Ethics Committee (EC).

In regard to OSs, and according to the Law no. 21/2014 of 16th April, they have to obey to the same criteria described for clinical trials, with the difference that it is not required the approval of INFARMED. Regarding the ECs, there is also a clear difference, since for OSs if the centre has its own local EC, this is considered a competent EC to evaluate the study. Nevertheless, if not, CEIC must be contacted in order to provide guidance on the adequate EC to be addressed.

2.5 CLINICAL RESEARCH IN PORTUGAL

In countries where clinical research has reached maturity levels, it turns the influence that the development of new drugs may have, for example in the continuing improvement of health care and quality of life of the population. Also contributing to the economic sector, particularly with the creation of wealth through the creation of direct and indirect jobs, the increase in GDP and improving trade balance, unfortunately this source of wealth is not being well exploited in our country.

In Portugal, clinical trials constitute the paradigm of clinical research, representing the biggest share of activity in this area.(42)

According to INFARMED data, over the last 9 years there has been a marked decrease in the number of clinical trials conducted in Portugal.

From 2006 to 2015 the number of CTs submissions decreased from 160 to 137, and fluctuated during this period, showing clear signs of stalling. Being that historic low was reached in 2011 with only 88 to be submitted to INFARMED. The average time of decision by the INFARMED has been improved over the years. According to statistics from own regulator, it was around 45 days in 2007, dropping to 28 days in 2015 (please see figure 5).(43)

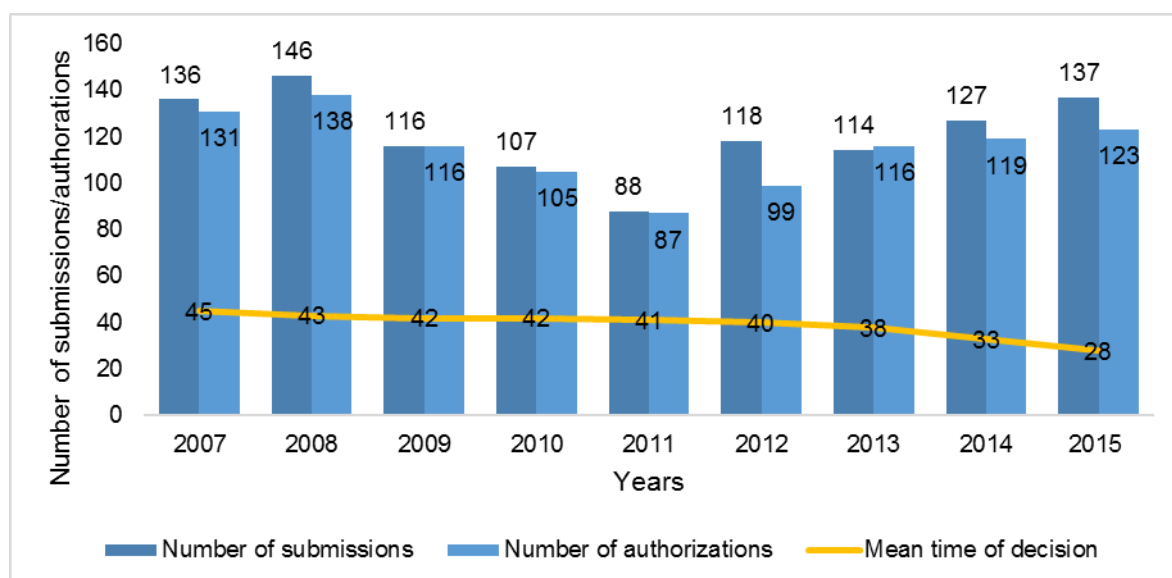


Figure 5. Number of Clinical Trial Applications submitted to INFARMED (2006-2015) and average time of decision (in days).(43)

Data from 2015 indicate that of the 137 submitted CTs, 65% are Phase III CTs (please see figure 6), and 64% of active substances of experimental drugs would be of chemical origin.

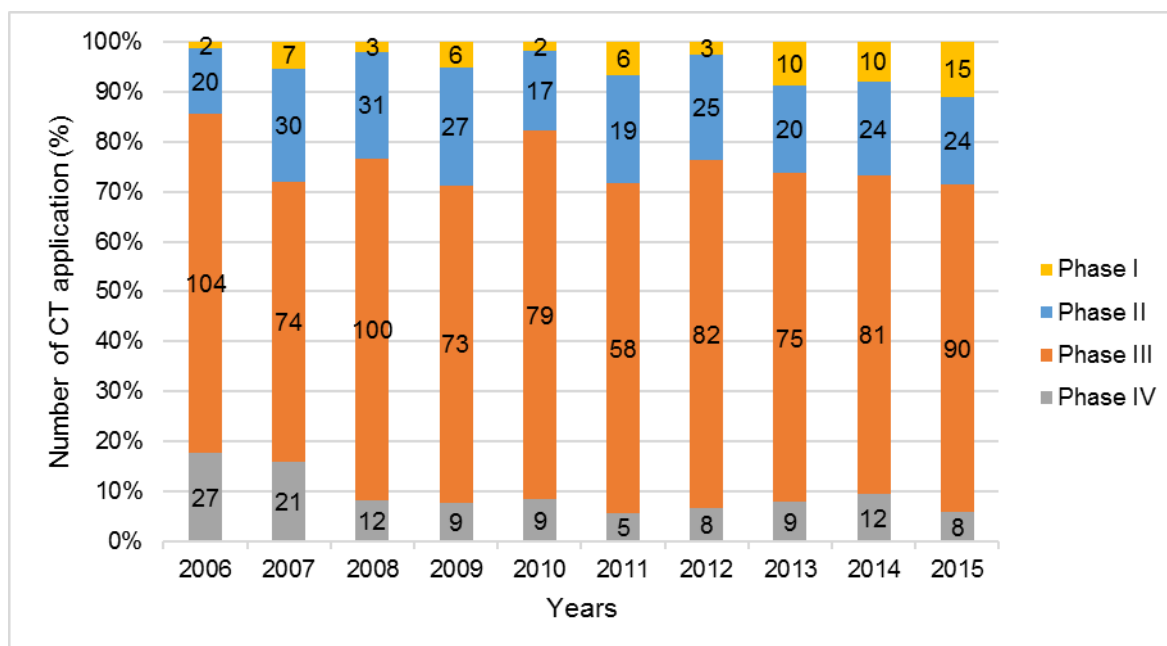


Figure 6. Number of Trials per Clinical Development Phase and year Submitted to INFARMED (2006-2015).(43)

At this time and according to recent statistics from INFARMED, from the beginning of the year to the third quarter of 2016, 20 Phase I CTs were submitted. Despite this slight increase over the previous year (15 Phase I CTs), it should be noted the low representativeness of phase I CTs (64 in 10 years).

Analysing the therapeutic areas covered by CTs submitted between 2007 and 2015, there is a clear predominance of antineoplastic and immunomodulators, followed by central nervous system and anti-infectives.

In Portugal, CTs are mainly promoted by multinational pharmaceutical companies (90% in 2015), on the other side the academic or investigator initiative CTs take on a residual rate. When compared to the European reference countries, Portugal has a modest performance both in number of clinical trials as the recruitment rates by CT. According to a study of APIFARMA conducted yearly, we can infer, according to 2015 data, that Portugal has 72% less on-going CTs than Belgium which is seen as a benchmarking country for Portugal due to developments in clinical research and its dimension which is similar to ours.(44)

For pharmaceutical companies the perception of a suitable environment for investment, is a key factor in the selection of the country that will receive the CT. In this decision are evaluated topics such as access to innovative medicines, or the price policy of the new drug. The environment for investing in clinical research in Portugal is anything but welcoming. As a result of the crisis, was necessary to impose reduction measures of public expenditure, which lead to successive price reductions of the reference medicines, which discourages investment for research and commercialization of new medicines. Other factors contributing to this negative scenario are: the lack of a development strategy for the sector, demonstrated by friction in adapting the regulatory framework to the requirements of the activity, the fact that the clinical research activities are not recognized as strategic for health care improvement, the clinical trial approval times are uncompetitive, the absence of legal deadlines for approval of financial contracts by the hospital administrations, which may take several months.(42)

It is imperative to shift this negative trend, since clinical research and, specifically clinical trials, may contribute with many benefits to social and economic development of countries like Portugal, such as:

Social Benefits

- Improvement of health indicators, since the new drugs resulting from this activity may provide advanced, effective and safer therapies for population;
- Earlier access to innovative therapies, through participation in CTs;
- Training and continuous development of medical investigators in the context of CTs; Scientific development, contributing to the creation of centres of excellence;

Economic Benefits

- Reduction of public expenditure, withdrawing burden to SNS treatments in CTs, funded by the promoters;
- Jobs creation in the research units of the pharmaceutical companies, as well as in Clinical research centres and CROs;
- Tax revenue, through direct and indirect taxes paid by companies of the sector;
- Improvement of the trade balance, guaranteed by exports made by multinational pharmaceutical companies with departments in Portugal and CROs;

In order to evidence the impact of clinical research in the Portuguese economy, in 2012:

- The investment done by multinational pharmaceutical companies amounted to 36 million euros;
- Reached a savings in public expenditure of 3.5 million euros;
- Generated a volume of tax revenue estimated at 7.5 million;
- The gross value added (GVA) reached 21 million euros.
- The employment data revealed the existence of more than 1,000 jobs dedicated to this activity in the same year.

In order to clinical research be able to evolve in Portugal, is essential to recognize that the creation of attractive conditions for the uptake of clinical trials requires, a converging vision among the several stakeholders (please see figure 7), including the Health Ministry, which should contribute to the definition of a government agenda and a strategic plan for the sector.(42,45)

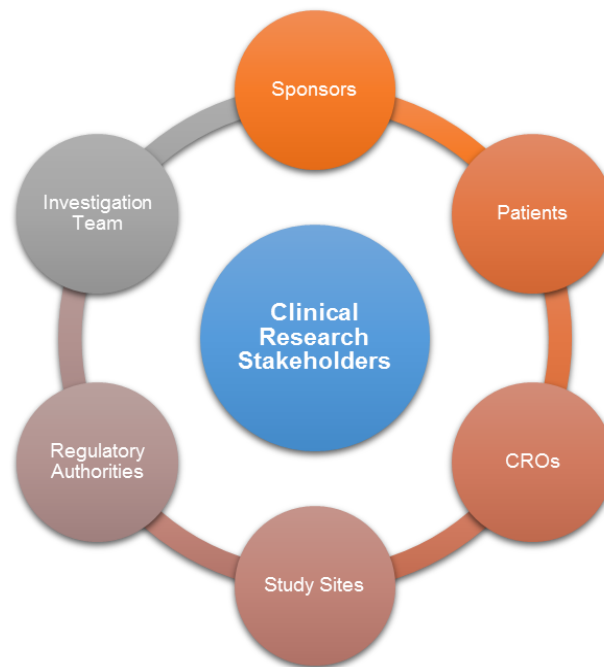


Figure 7. Stakeholders of Clinical Research.

2.5.1 CONTRACT RESEARCH ORGANIZATIONS

According to the Guideline for Good Clinical Practice (GCP) E6 (R2), CRO is "a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions". Being that sponsor is defined in the same as guideline as "an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial".

Historically, outsourcing activities of drug development to external entities goes back to the 1940s and 1950s. In this period, Huntingdon Life Sciences and Charles River Laboratories provided animals to be experienced, or conducted the tests themselves. Only in the 1980s and 1990s with the arrival of the stream of blockbusters drugs by pharmaceutical industries, CROs began to grow and be recognized as strategic partners, which did not happen previously due to concerns about the quality and scientific expertise. CRO's services accounted 4% of R&D of spending of pharmaceutical industries in the early 1990s, and increased to 50% in mid 2000s.(46)

The relationship between the clinical study sponsor and the CRO has also evolved over the course of time. For the first two decades of the CRO industry, CROs were treated like “order takers”. With the experience and maturity brought upon by time, CROs switch from mere service vendors for trusted partners.

This evolution was naturally impactful to the market size and growth. In December 2007, Goldman Sachs estimated that the Phase II-III outsourcing market would increase roughly 16% from 2006 to 2011 and estimated the total CRO market to be worth over US \$29B annually in 2011.(47) According to another report from business information provider Visiongain, revenues for CROs are expected to reach \$32.73 billion in 2015, with the industry pursuing this route thanks to its ability to drive cost advantages and offer regional expertise by way of its research service providers.(48)

The core services provided by most CROs, like those already described in the description of W4R are: project management, clinical monitoring, investigator and patient recruitment, data entry & validation, database design & build, regulatory affairs, post-marketing surveillance, safety and pharmacovigilance, statistical analysis plans and reports, final study report, among others.

It is important to discuss the objectives, costs and steps towards the CRO, so that stay all defined before making any contractual commitment. Sponsors should audit the CROs to ensure the quality of services.(49)

3. ON-THE-JOB TRAINING

This chapter is intended to describe the activities developed during the 8-months internship.

My internship was developed mainly in the field of observational studies, since they constitute the largest share of W4R studies. This had a positive side, since it is a good way of adaptation to the clinical research context, once that the monitoring of most observational studies is less demanding methodologically, compared with clinical trials. They not involve experimental medication or any other intervention in the patient beyond the usual clinical practice.

The main focus area of my training was the activities typically assigned to the Clinical Research Associate (CRA). Despite of this, my internship included a junction of several areas of clinical research allowing different experiences, which became in a higher gain of knowledge. In this chapter I will describe the procedures followed during the internship to perform the requested tasks and introduce the different areas of work.

The chapter is divided in two sections: specific training - clinical monitoring and other clinical research related activities. Each subsection is a more detailed description of the activities developed.

3.1 DISCLAIMER

For being part of W4R I had to sign, at the beginning of the internship, a confidentiality agreement concerning sensitive and confidential information that I would manage working as a CRA trainee. That said, there is some information on the studies with which I had contact that I cannot share.

3.2 ARRIVAL AT THE INTERNSHIP ORGANIZATION

In my first day of internship - November 2, 2015 - I was very well received by members of the W4R team. After a briefing of the office features and work habits, was given me the material needed to carry out my activities during the internship. In my early days there I spent most of my time getting familiarized with the structure and operations, by reading the quality manual and Standard Operating Procedures (SOP) of W4R. During the first week, I had a meeting with my internship supervisor, who is the Head of External Affairs of W4R, in which was presented my internship plan with the topics I would receive training, such as general information of W4R, clinical studies focused on monitoring, types of studies and methodologies, applicable laws and guidelines and medical writing. Featuring then the practical application of this knowledge acquired, with activities like submission, initiation and monitoring of observational studies, as well as, medical writing

tasks such as the development of Case Report Form (CRF), Informed Consent Forms (ICF) and other work. Ending with the note that this plan could change, considering the uncertainty of the projects that W4R could come to acquire, as well as their requirements.

3.3 SPECIFIC TRAINING: CLINICAL MONITORING

3.3.1 THE CRA ROLE

Every clinical study requires monitoring. According to ICH-GCP monitoring is defined as "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s)." (34)

As so, the monitor has a crucial role in the proper conduction of a clinical trial, as well as several responsibilities. The monitor needs to ensure that, above all aspects, the rights and safety of the subjects are guaranteed. Besides, the monitor also assures that the clinical trial data are complete, accurate and supportable by source documents, as well as, that the conduct of the trial is in compliance with the currently approved protocol/amendment(s). (34)

Before choosing the internship, I had no work experience in clinical research, thus I want to realise a multidisciplinary internship in the different tasks of this area. However, my main area of interest and which resulted in a greater focus during the internship was the clinical studies monitoring. The main reason that led me to embark on this area was the fact that it is extremely important in clinical research where much money is invested and which are expected brilliant results, bringing great benefits to the health of patients, changing their lives.

When I was integrated into the scientific department of W4R as a CRA trainee, it was allocated to me two OS in Asthma and Myelodysplastic Syndrome. In both I assumed functions of CRA, always with the supervision of the Clinical Project Manager (CPM), of each study.

In the performance of CRA role it has to be the ability of motivate and organize the study team as well as a leading role in planning, coordinating and monitoring all the study procedures. It also is necessary to have a bunch of soft skills that are the key to achieve success on managing interpersonal relationships.

In addition to the functions and responsibilities mentioned above, CRA is the main line of communication between the sites and the sponsor; performs site management not only on-site but also from the office (in-house management); review study data from the subjects and verifying it against source data and collecting for processing; Liaising with ethics committee and regulatory authorities, internal departments and suppliers.

3.3.2 SITE START-UP: FEASIBILITY AND SELECTION

In order to perform site and Principal Investigator (PI) selection, are taken into account factors such as the total number of patients to be recruited; total and regional prevalence of required condition or disease; sites and/or PI given by the sponsor; specific requirements of each site; good past experience with the site and/or IP. After identification of site/investigator with sponsor's approval, is carried out an initial contact with the potential PI, presenting the study generally, assessing the interest and availability to participate. If expressed interest, is requested the signing of a confidentiality agreement. Next is done an evaluation site/investigator which may be made through a feasibility questionnaire, at distance, or through a site visit. Through the collected information and taking into account the site's approval time; the experience of the investigator; the potential for recruitment and the availability of the investigator, is making the final decision.

During my internship, between the months of January and March of 2016 I collaborated actively in the selection of sites and investigators of the study on the asthma disease. In this case the sites were designated by the sponsor who also made a first contact with the service director (SD) of each site. In some of these sites the sponsor was able to set the IP, sending us his contacts, in other sites I had to firstly contact the SD.

Using the strategy defined by the CPM, I started to make contacts with SDs, by email, which had attached general information of the study. Later I performed telephone contacts to assess once more the interest and availability to participate in the study. After positive feedback, I asked who would be the PI, and requested his contacts. With all the PIs defined, I scheduled a date for a pre-study visit to the site. This is a visit on site with the objectives of formally present the study, clarify any doubts and discuss the strategy to implement the study on the site. I followed my CPM in six pre-study visits, preparing all background documentation, having conducted one visit on my own. At the end of each visit, it was up to me to draft the respective visit report on W4R forms.

3.3.3 SUBMISSION TO COMPETENT AUTHORITIES

It is part of the monitoring activities the preparation and submission of the OS to the regulatory authorities (see chapter 2, section 2.4.2). According to the Portuguese Law 21/2014 of April 16th, when a sponsor wants to perform a OS is only necessary submit the study to CNPD and Ethics Committee (EC) & Administration Board (AB) of the site.(7) Submission to the CNPD is made through an online form and should be prepared according to their requirements. The documentation requested by CNPD should be sent along with the submission form, or later by e-mail with the file number.

The submission dossier must be prepared by the CRA and revised by CPM, in accordance with the requirements of the sponsor and site. If, during the approval process, the site sends questions about the project, the CPM shall immediately notify the sponsor, and all the information to the site should be provided with as soon as possible.

During the first month of the internship, I participated in the submission of an OS on myelodysplastic syndrome to CNPD, accompanying and collaborating with CPM in filling out the electronic form.

Retaking to my experience during the internship with the study of asthma, after the selection of sites, I started collecting the necessary documentation from the IP and DS involved. Whenever possible were collected some documents during the pre-study visits. At sites where this was not possible, I made frequent contacts in order to gather all the necessary documents for submission. Some hospital centres, have their own forms to be used. These forms are usually own models of financial agreement, requirements for AB and/or EC and cover sheets/presentation of the study. In these situations, it was necessary to fill out and collect signatures of the PI.

Once in possession of all necessary documentation and applicable to each site requirements, duly completed and signed, I prepared the submission dossiers. In general, a submission dossier contains the following documents:

- Contact list - representative of the sponsor, representative of W4R and IP;
- Requirements - addressed to EC, the AB and, where applicable, to clinical research support office;
- SD authorization;
- CNPD authorization;
- IP Curriculum Vitae;
- Protocol signed by PI;
- CRF or the variable list;

- ICF;
- Declaration of absence of financial agreement, because this study did not include payments to the site.

In this study, which was submitted to public and private sites, I realized that depending on the site there are differences in the delivery point and with forwarding of the process. Might happen the following situations:

- Submission to AB - dossier forwarded to the EC for receiving their seem, and then returned to the AB to be evaluated;
- Submission to EC - gets their seem and subsequently is forwarded to the AB for final evaluation;
- Submission simultaneously to AB and EC - is necessary to submit two dossiers, however, the CA issues their assessment only after consideration of the EC;
- Submission to specialized research offices - first evaluated by these before being sent for consideration of the EC and later, AB.

Once submitted the study to the responsible hospital entity, I kept regular contacts in order to follow the evolution of process.

Since the studies are constantly evolving and not being unchangeable, when it finished the first version of the essential documents - synopsis and Protocol; ICF and CRF - is quite common to do amendments to the protocol which can be substantial or non-substantial amendments. It is important to note that, every time that is needed to undertake a substantial amendment is necessary to submit these changes, for approval, to the competent authorities. The main difference between the two types of amendments is that for one to be considering as “substantial” it has to be likely to have significant impact on the patient’s safety, mental and physical integrity or on the scientific value of the study. The substantial amendments that I had performed were made in the study of asthma, on the scope of a change on the PI, and when was made an amendment to the protocol, which implies to new versions of the ICF.

Table 1 - Substantial and Non-Substantial amendments requirements on Observational Studies.

Substantial	Non-Substantial
<ul style="list-style-type: none"> ▪ Changes to the primary or secondary objectives of the study; ▪ Change of study population, or the sample size; ▪ Change of PI; ▪ Change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment; ▪ Change the data sources and/or the method of data collection. 	<ul style="list-style-type: none"> ▪ Changes to the identification of the study (change of title, etc.); ▪ The addition/deletion of exploratory/tertiary endpoints; ▪ A minor increase in the duration of the study (<10% of the overall time of the study); ▪ Minor clarifications to the protocol; ▪ Correction of typographical errors.

The final step of the study submitted to the hospital's competent authorities was the receipt of the craft confirming that the study was approved by the EC and AB of the site.

From that moment, the conditions are met to conduct the Site Initiation Visit (SIV) in order to start the study on the site.

3.3.4 MONITORING VISITS

According to Law 21/2014, April 16th, the monitoring person (commonly designated by CRA) is responsible for guarantying that the data is correctly and completely recorded and verifies if the storage, distribution and returning of and documentation of the materials under research comply with the good clinical practices. To do this, CRAs perform Source Data Verification (SDV) which is the act of compare the data present in source documents against data registered in the Case Report Forms (CRFs). The sponsor usually defines the number of visits performed during the clinical trial. There are different types of site visits: site selection, initiation, monitoring and close-out.

3.3.4.1 SIV–SITE INITIATION VISITS

After the authorizations to perform a clinical study are granted and when the necessary conditions to perform the study at the study site are verified, a Site Initiation

Visit (SIV) is performed by the CRA. A SIV is most alike a kick-off meeting of the project and it is performed to ensure that all investigators, co-investigators, and other study staff members are fully informed about their responsibilities and obligations, concerning a clinical study and are fully prepared to conduct it according to the protocol and ICH-GCP guidelines.

Between April and June, as part of the study on myelodysplastic syndrome, I closely followed initiations of some sites. After obtaining the authorization for each participating site and the financial agreement signed by all parties (this study involved the payment to site), I started preparing SIV. Started contacts beforehand in order to bring together all investigators belonging to each site investigation team during the visit. I prepared a Power Point presentation, to support the SIV, which covered the following topics: protocol review; study design; inclusion/exclusion criteria; schedule procedures and monitoring plan; GCPs; AE&SAE reporting and an introduction to eCRF.

In an OS, all the information and documentation necessary for the beginning of it, are compiled in the Investigator Site File (ISF), also known as investigator dossier. I prepared the ISF before all SIVs I attended and, usually, are part of it the following documents:

- Contact list - sponsor, CRO (CPM and CRA) and IP;
- Protocol and its amendments, if applicable;
- Protocol signature page;
- Copies of the ICF;
- Forms to register the evaluated patients (screening log) and patients included in the study;
- Copies of CRF or list of variables and questionnaires, if applicable;
- Authorizations of the relevant regulatory authorities - CNPD, EC and AB;
- Authorization of the SD, where the study will take place;
- Confidentiality agreement;
- Financial agreement signed by all parties;
- Safety, notification form for Serious Adverse Events (SAE) to Competent Authorities;
- Regulatory documents, as the CVs of all team and specific forms of the site;
- Forms, aimed to record the: visits of monitors to the site, responsibilities and training of each investigator;
- Correspondence between: sponsor, CRO and site.

A few days before the SIV should be sent a confirmation of the visit by email. The SIVs I attended were conducted by CPM, which presented, all the information contained in the power point (explained above), the ISF and also gave training in the data base (eCRF). At the end of training, I collected copies of some documents, such as, signed visits log, responsibilities registration filled, the CV of site team members, completed training log, reference values of the site laboratory. Additionally, I requested the email addresses of investigators, later to be sent to them the access credentials to eCRF. From the moment you end the SIV, it is considered that the study is officially started and that are all the conditions to start recruiting patients.

After each SIV I attended, I drafted the report of the same, the forms of W4R, which until after being reviewed were sent to the sponsor.

3.3.4.2 SMV – SITE MONITORING VISITS

For the monitoring purpose, all source data must be available for monitoring by the sponsor (or its designees), inspections or audits of Health Authorities. Source data can be defined as all comprised of documents that are the first point of entry of patient's medical records.

According to ICH-GCP, source documents are *“original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)”*.(34)

The first Site Monitoring Visits (SMV) should be carried out as described in the monitoring plan, or as a set with the sponsor. If this is not described, it is recommended that the first SMV arises as soon as possible after the inclusion of the first patient or if they have not been included patients, 2 months after the initiation of the site.

The number of SMVs varies according to the type and characteristics of the study. Usually the sponsor defines this number, but it may require some adjustment as the study proceeds, especially if the recruitment rate at a specific study site varies from what was expected, or if there have been a number of issues and protocol violations discovered in previous visits. The SMV related activities start before the visit itself, by performing the necessary activities for the visit (preparing documentation, scheduling the visit with the investigational team, assess the recruitment rate, among others).

During the SMV the main activity is CRF review and SDV, meaning checking if the data within the CRF of the study is in accordance with the source medical documents of the patient. In addition, it is checked if the CRFs are being completed and if they are accurate, consistent, legible (not applicable to eCRF), dated and signed by the investigator. This can only be done after checking if the patient has signed the informed consent form.

Furthermore, it is checked if they are to comply with the protocol and with the GCPs; check the recruitment rate, comparing the expected patients with already recruited; ensure that the ISF is complete and up to date; confirm that the queries were resolved in a timely manner and motivate the team to recruit, to meet deadlines and the need for data to be complete and quality. Check if any element was added to the team, if so, to ensure receiving the proper training, meets the regulatory requirements and verify that the essential documents are properly updated.

At every SMV is important to confirm patient's safety, and to do so is necessary to verify if any Adverse Event (AE) occurred and if it was registered on the eCRF. In case of SAEs is needed to assure that the event was reported to the pharmacovigilance department within 24h.

After these visits a monitoring report is prepared and sent to the sponsor.

During my internship I did not have the opportunity to perform any SMV, however, I acquired theoretical knowledge concerning this, receiving training in the W4R's SOPs.

3.3.4.3 COV – CLOSE-OUT VISITS

This is the last monitoring visit that is made to study site. First of all, the study site may be closed for some reasons, including: the study is complete in accordance with the provisions of the protocol; IP request for personal or associated with the site impossibilities; problems in recruiting patients; Major non-conformities; cancellation of the study by the promoter.

COV has to be carried out for all sites that have been initiated, even when no patients were recruited, and is performed in order to guarantee that all investigators, co-investigators, and other study staff members are fully informed about their responsibilities and obligations concerning the archiving of essential documents, according to the ICH-GCP guidelines. The visits are performed once the last patient has completed the study, performing all follow-up procedures and all CRFs have been completed. Before the COV, the CRA should review the Site Master File (SMF) to identify any documentation that may be missing.

During the COV, CRA should do the following procedures:

- Check if all forms are complete;
- Confirm that all ICFs are properly filed;
- Check if the source documents are updated, complete, according to the monitoring plan and properly filed;
- Check that all CRFs are complete, signed and available in the site, and all queries are resolved and signed;
- Check the safety aspects;
- Check that the ISF is complete and ensure that the dossier complies with the SMF;
- Compile dossiers of the study, seal up and notify the archive period of the site (5-year OS, 15 years for CT or as requested by the sponsor);
- Notify, AB, EC and PI on the study closure, making a short summary of the same, relative to the site.

Just like all other monitoring visits it is necessary to elaborate a close - out visit report, which will be sent to the sponsor.

3.4 OTHER CLINICAL RESEARCH RELATED ACTIVITIES

3.4.1 MEDICAL WRITING

Medical Writing (MW) involves a set of activities related to the communication process of clinical and scientific data. MW implies the need to combine scientific knowledge with the capacity to search information with the discernment on how best to present it, directing it in the best way for each target audience. Thus, the final communication of a study should reflect all work developed, constituting the fundamental tool in the dissemination of the results achieved. Hence the quality and clarity of the disclosed information are fundamental for the recognition of the study. In addition to traditional tasks of MW, I developed other, aimed to marketing area. So I divide my experience in MW in two sections: medical / scientific and marketing.

3.4.1.1 MEDICAL/SCIENTIFIC

Medical Writing is an integral part of clinical research and revolves around project documents and its activities include documents development, management, review and approval. It is a very important activity in clinical research since the success of a project highly depends on the array of documents that support it at any point of development.

As mentioned above in Chapter 1.2, W4R has the MW service, allowed to provide the client documents such as: Synopsis and Protocol; Variable lists/CRF; Package Insert and

ICF; Final study report; Reports of advisory boards, panels or experts focus groups; papers; abstracts and posters; clinical cases; disclosure documents of clinical and scientific information, documents translation.

During my internship I had the opportunity to participate in some MW activities. Early on, in November I made a Portuguese translation of a synopsis, related to an OS that was written in English. This task showed me that in MW the word that prevails is rigour, since it is about written communication, the slightest mistake, however slight, can lead to different interpretations, and lead to failures in the future. Even in the first few weeks of the internship, I was asked to do a critical review of an eCRF, a task that was extended for two studies. I performed a check between all parameters evaluated in the lists of variables and the parameters present in the eCRF. I then tested the eCRF to suggest strategies to make it as user friendly as possible, in addition to checking all eCRF validations and suggesting new ones, based on information present in the protocol, such as the eligibility criteria. Although this task was not of MW, it allowed me to have contact, to know how to interpret and to know the organization of essential documents.

During the month of February, I had the first contact with an ICF, in the framework of an observational study, being involved in the writing of the ICFs. Based on a W4R template, four versions of ICFs were written for: adults, under 16 years old, aged 16 or over and parents / legal representatives of minors.

In April, the need arose to write a protocol for a new OS, and I was asked to make the introduction and the rational of the project. To accomplish this task, I began by doing some basic research on the disease, in this case Asthma. This was a very enriching task, since when I finished writing these chapters, a meeting was held together with the project manager, in order to jointly review the work. After some brainstorming and clarification, I realized that I had made some shortcomings, especially in the transition from introduction to rational, and even in choosing the topics of the project rationale. I left the meeting with new strategies and tools to apply in the future.

In the final phase of the stage, I still required to experience the initiation of a clinical study, to find strategies of implementation in the centres, to think the own study design, and to write all the essential documents from scratch. It was then that this possibility arose with a new client, who hired W4R, to implement a study in the area of Diabetes mellitus. I was assigned together with a colleague to the study, and after some meetings in which the guidance provided by the sponsor was discussed, and the implementation strategy, study design and some objectives defined, we began to write the essential documents. In order to write the protocol, we have previously read and reviewed the literature provided

by the sponsor about Diabetes, regarding the statistical data of the disease, prevalence, European and national treatment guidelines, and some articles on similar studies. We used the W4R template to write the protocol, having some doubts when defining primary and secondary objectives, as well as the endpoints and eligibility criteria. After we had completed a protocol draft, the sponsor requested that it be written on their template. The task of transferring the information from one template to the other turned out to be complex, such were the specifications of the sponsor's template. Once finished the protocol and its synopsis, we composed the ICF and the list of variables. Constructing the list of variables, it was necessary to do a thorough search of all the therapeutic alternatives, drug classes and doses. The follow-up of this early phase of the study was a very useful learning moment, in which I understood how the study protocol was conceived, and even the study itself, and then the application of MW techniques in the preparation of the study documents.

3.4.1.2 MARKETING

I've been involved three times during the internship, in this type of writing, always for the same client.

The aim of the service was to hold a document in PowerPoint on a specific product and the associated pathology, for distribution to the client's sales force in order to have a better scientific support when submitting the product to the physician population.

Started with the collection of information from references relating to pathology and analysing the supporting material delivered by the about the product. Following the development of the Power Point document, in which I felt some difficulties, summarize information frame in schemes in order to facilitate visualization and knowledge retention on the part of interlocutor. Once developed the document, it was reviewed by a colleague of MW and the project manager, who gave me their feedback.

I felt a great evolution in the following work I have done in this area since it became quickly put the information on schemes.

3.4.2 QUALITY AND AUDITS

Quality is a key factor for a good development of clinical trial related activities. If the trial is not based on a good quality system the data cannot be considered accurate and reliable.

I had the opportunity to follow two audits. The first was an internal audit, conducted by an independent entity, in order to test the Quality Management System (QMS) implemented by the W4R management team. Internal audits are planned annually by the

top management through an Audit Program as indicated by the ISO 9001. It is top management responsibility to define the dates of the internal audits, adequating the program to the company activities and communicate their program to all the employees. The auditor, responsible for the internal audit, is chosen by the company in accordance with the requirements included in the QMS.

The second was an external audit performed by a client. The client was an multinational pharmaceutical, and the purpose of the audit was to verify if the W4R had the expected requirements to continue performing the monitoring of an OS which it had been developed by W4R from the beginning and was in the sites implementation phase, as well as, future studies that could arise.

4. COURSES

Between the months of November and December, W4Research offered to their collaborators a course of *CaFe – Centro de Apoio e Formação Empresarial, Lda (CaF)*, entitled “Marketing and Management”. This course was divided into three curricular units: Pharmaceutical Marketing; Digital Marketing and; Accounting and Management. The course duration was 50 hours, it was intended that, with this training, the participant will acquire competences in order to:

- Framing Marketing with Company Strategy;
- Define selection and targeting criteria for markets and customers;
- Identify essential tools of Digital Marketing and its functionalities / objectives;
- Adapt Digital Marketing to strategy;
- Create, configure, manage and publish corporate social networking pages;
- Know the Standardization of accounting in Portugal;
- Understand the main financial statements;
- Calculate Net Income for the Year;
- Analyze the financial situation of a company, assess the risks incurred, the real profitability and its capital structure;
- Dialogue effectively with financial partners.

4.1 PHARMACEUTICAL MARKETING

In the unit of Pharmaceutical Marketing, were taught, the basic concepts of marketing, the difference between this and pharmaceutical marketing (specificities), was explained the proximity of marketing to sales and defined the difference and between product marketing and service marketing. Regarding the market, was presented, the business in the context of "B2B" and "B2C", the pharmacopolitical environment, the competing market analysis and SWOT analysis.

4.2 DIGITAL MARKETING

In the following curricular unit, we explained the evolution of digital marketing, and its potential when at the service of the company's strategy. An approach was presented in which digital marketing was integrated into the overall marketing plan. Digital marketing as a key point in the internationalization of a company. We also introduced the various tools of digital marketing, social marketing, search engine optimization, relative to google.

We learned to enhance the presence of companies, products and brands in the online medium. In an age increasingly globalized and technologically advanced the need arises, by the companies to position themselves online as a way to reach your customers 24 hours a day. At the internship, I applied the knowledge acquired in this training, to create the LinkedIn page for W4R.

4.3 ACCOUNTING AND MANAGEMENT

In the last curricular unit, we learned all the accounting information, from the objectives and divisions of accounting, to company flows, financial and economic information tables and complementary information tables. In the context of the accounting method, we learned to read the account and launch, the trial balances. We learn to read the wealth masses, such as, assets, liabilities and equity; And to analyze the balance sheet accounts. The composition of the net result in the income statement and in the balance sheet. Regarding the presentation of the accounts, the complementary documents were presented:

- Management report;
- Legal Certification of Accounts;
- Report and Opinion of the Supervisory Board or of the Sole Auditor;
- Act of approval of accounts;
- The official models: Model 22, the simplified business information and its annexes.

As regards the organization of the financial function and the basic financial concepts, the relationship between the financial function and objectives of the company, the real and financial flows, the accounting versus the financial view, and the preparation of the accounting information for analysis. The parameters of the financial analysis to be analysed, such as liquidity, profitability and / or safety, were also pointed out.

The certificate of vocational training related to this course is found in the chapter of the annexes.

5. DISCUSSION

This chapter presents the discussion of features of the internship activities developed and my point of view of the outcomes and objectives achieved.

Having the opportunity of taking part in an observational studies team was a pleasing experience, not only because of my professional growth but also because it allowed me to face some adversities and learn how to overcome daily obstacles which made me grow professionally and personally.

During the internship, it was possible to have relatively broad contact with the areas of expertise and services provided by W4Research. This was achieved both through the activities and tasks carried out under the monitoring of observational studies and medical writing activities, but also have some contact with data management, through internal training of W4Research's procedures, development of variables lists, revisions of databases, and then in practice as CRA, in solving problems identified by site investigators with data entry.

When I firstly contacted with observational studies, I didn't have much background on these, since my theoretical training was very focused in clinical trials. Nevertheless, I quickly realized the differences between OS and CT, in terms of objectives, duration, budget and regulatory requirements. My interest in this type of studies has increased, due to their importance in studying diseases following the progress of those in the population, or to evaluate the drug route already approved for the market. I also find very catchy the fact that through observational studies we can get data and conclusions of the effective population, following the clinical practice, as opposed to the controlled environment necessary in the practice of clinical trials.

It was also important to know in practice the function of a CRA, since with the theory is difficult to have a sense of what are in fact its daily activities. I was having some difficulties in the course of the CRA role in particular in establishing contact at a distance, by email or telephone, with service directors, and were common the examples of unanswered emails, rejected calls and no return of it. Sometimes when the contact was achieved on a regular basis, was the invocation of lack of time, unavailable by personal and / or hospital staff issues, to justify the absence of interest in participation in a given study.

These are some of the difficulties we went through, and that part of the life of a CRA, which is to achieve in the short time we have during the contact with service officers, motivate them to participate in the study and to form a dynamic team in service. For this it is essential to be assertive, to focus on the key points in the short time that is available and demonstrate a full knowledge of the study that is presented.

Several professionals agree that the first and foremost problem shared by observational studies and also clinical trials, lies in the choice of sites and inadequate management of the project. The phase of site authorizations is always critical to a study. Both the sponsor and W4Research set goals and deadlines for approval and often, sites do not work with the pace and with the proper interconnection between the actors involved so that this process runs smoothly. In addition, it often happens that local EC raise questions and objections to certain points of the study. Some of the time, by sheer lack of attention in the analysis of the documents submitted. The process of receiving the questions, preparation of responses, sending and evaluation of these, entails substantial delay the approval process. When, and running everything nearly perfectly, the process would last between month and a half to two months to EC and AB approval, can, relatively easily, be extended to five months. This situation is unaffordable for those who need to implement a study. This situation leads to, that some study sites begin to screening and recruit patients at different times, having sites beginning weeks or months later than others. This heterogeneity in the timing of approval, between sites, can lead to recruitment failure.

Another point that I learned how to do was the Financial Agreements between sites and the sponsors. It was challenger, because it is a long and bureaucratic process in which every single detail of the study part has to be agreed by each part. It is necessary to be aware of the site requirements about study fees, as well as, already available templates the sites may have. It is also important to have input from the investigational team about the distribution of the fees amongst them and, to make sure that all involved parties are contemplated in the agreement. Some sites are easier to handle when it comes to contracts since they have few specific requirements. But in other cases, the process can take months until it is finalized which is another fact, contributing to the delay of site initiation. So to increase the motivation of investigators and research teams, it should be more specific the payment of these professionals and should be better established between the sponsor and the administration board for this part would not be lost in the financial contract. I think it calls for a standardization of financial contracts approved only by one national entity in order to minimize differences and deviations.

All this makes Portugal to be an unattractive country on the sight of the multinational pharmaceutical companies, which lose the will to implement their studies in our country.

Overall I enjoyed the experience as a CRA, I am aware that I have yet to experience many situations and activities, and have contact with clinical trials, which at this internship I had no opportunity to do.

I enjoyed a lot going to sites and understand the site's environment that is lived by investigators and study coordinators. That made me understand more the other partner that are the study teams and comprehend better their requirements and their work practices. I realize that the relationship established between the study teams and the CRO/sponsor is an important component to fluidize the process in order to achieve the timelines provided.

The experience of 8 months' internship at W4Research gave me the development of skills, both personal and professional level.

In the personal skills I would highlight:

- Adaptation to new contexts: new city, professional environment;
- Time management, planning and setting priorities, when there are several situations to meet in a given period of time;
- Fulfilment of tasks / activities in accordance with procedures and deadlines;
- Management of different personalities, when the work is performed in a team and we need to get together a certain result;
- Take the initiative, to have vision, be proactive and self-critical in the tasks performed;

In the professional skills I would highlight:

- Practical knowledge of the work developed by a CRO;
- Knowledge of legislation and national and international regulations applicable to clinical research;
- Knowledge of the processes and procedures associated with the role an observational studies monitor;
- Preparation of studies submissions to national authorities and research centers;
- Development of financial agreements;
- Preparation of pre-study and site initiation visits and its reports;
- Valuing the importance of having all registered and duly archived information, since what is not written, for regulatory and legal purposes, did not exist;

- Ability to solve problems, both independently and in conjunction with the sponsor, with the centers and research teams;
- Working with multidisciplinary teams;
- Working with electronic databases to support research;
- Communication skills, both face-to-face and remotely, with the centers and research teams;
- Knowledge of therapeutic areas and pathologies associated with studies followed;

At the end of this internship, it must also highlight the important contribution of all who surrounded and helped me at W4Research in a personal and professional development level. I matured and acquired new knowledge and experience, trying to leverage strengths and improve weaknesses with a view to entering the job market.

6. CONCLUSION

From 2 November to 30 June was given to me, the opportunity to perform an internship at W4Research.

Overall, I think I achieved both primary objectives, of understanding the CRA role and the dynamics of CRO work environment. Now I can say that I know by experience and not just by theory how it is the lifestyle of a CRA. It is a very challenging role, be in permanent contact, supporting the sites, solving problems that arise in the course of the studies. In executing the CRA paper, I highlight the fact that, with the conduction of activities on site and/or in the office, it never becomes a boring routine.

Revisiting secondary objectives, I think we also have been fulfilled, however, the quest for knowledge is an endless process, there is always something new to learn and, in addition, clinical research is an area in constant change, whether the level paradigm, such as regulatory or new discoveries, so we must be very attentive to the news. To better understand the business model of the pharmaceutical industry, it has greatly contributed not only involvement in studies promoted by them, but also the sharing of knowledge among W4Research collaborators. Regarding the interpersonal skills, it is something we are always evolving, and consolidate. I need to improve on a daily basis, for example my assertiveness skills and better planning and prioritization tasks.

At the end of this stage, it must also highlight the important contribution of all who surrounded me and helped in my personal and professional development.

I matured and acquire new knowledge and experience, trying to leverage strengths and improve weaknesses with a view to entering the job market.

After the internship finish, I was informed that W4Research was interested in doing a professional traineeship with me.

I am truly grateful to W4Research for welcomed me and let me be part of their team.

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ANNEXES

Annex 1: CaF Professional Training Certificate

Certificado de Formação Profissional

Certifica-se que Tiago Emanuel Costa Marques natural de Leiria nascido em 11/01/1993, com o N.º de Identificação Civil 14135701 válido até 10/02/2017, concluiu com aproveitamento o curso de Formação Profissional de Marketing e Gestão, em 17/12/2015, com a duração de 50:00 horas.

Unidades de Formação/Módulos/Outras Designações	Horas (hh:mm)	Classificação
Marketing e Gestão	50:00	-

Flamenga, 24 de maio de 2016

O(A) Responsável pelo(a) CaFe - Centro de Apoio e Formação Empresarial, Lda

(Assinatura e selo branco ou carimbo da entidade formadora)

Certificado n.º 178/2015 de acordo com o modelo publicado na Portaria n.º 474/2010

