Universidade de Aveiro
2020/2021

Ana Raquel Neves Brito

RELATÓRIO DE ESTÁGIO CURRICULAR NUMA CRO: ASSUNTOS REGULAMENTARES E FARMACOVIGILÂNCIA
COORDENAÇÃO DE ESTUDOS CLÍNICOS

REPORT OF A CURRICULAR INTERNSHIP IN A CRO: REGULATORY AFFAIRS AND PHARMACOVIGILANCE
STUDY COORDINATION

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REPORT OF A CURRICULAR INTERNSHIP IN A CRO: REGULATORY AFFAIRS AND PHARMACOVIGILANCE STUDY COORDINATION

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção de grau de Mestre em Gestão da Investigação Clínica, realizado sob a orientação científica da Prof. Doutora Maria Teresa Ferreira Herdeiro, professora auxiliar do Departamento de Ciências Médicas da Universidade de Aveiro.

Curricular internship report presented to the University of Aveiro to fulfil the necessary requirements for the Master's Degree in Clinical Research Management, held under the scientific guidance of Maria Teresa Ferreira Herdeiro, assistant teacher at Health Sciences Department of the University of Aveiro.

“Tudo posso Naquele que me fortalece”

Filipenses 4:13

o júri

presidente	Professora Doutora Sandra Maria Tavares da Costa Rebelo professora auxiliar da Universidade de Aveiro
vogal - Arguente Principal	Doutora Emília Maria Gonçalves dos Santos Interna de Formação Específica em Medicina Geral e Familiar, Usf Modivas; Aces Grande Porto Iv
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A Deus porque por Ele todas as coisas são feitas.

palavras-chave

Estágio curricular, Investigação Clínica, Assuntos Regulamentares, Farmacovigilância, Linhas de orientação, Coordenação de estudos, Legislação

resumo

O presente relatório foi realizado no âmbito do Mestrado em Gestão da Investigação Clínica, realizado entre outubro de 2020 e abril de 2021. Começa por enquadrar a área de assuntos regulamentares e farmacovigilância no campo da investigação clínica. Destina-se, também, a reportar as atividades realizadas durante o estágio curricular na BlueClinical. Durante o período de formação, foi possível o desempenho de funções inerentes às diferentes atividades da equipa de assuntos regulamentares e de farmacovigilância. Para além disso, houve ainda a oportunidade de desempenhar atividades referentes à posição de coordenação de estudos clínicos no Centro Hospitalar Baixo Vouga. Tudo isto, permitiu a aquisição de conhecimentos práticos na área de investigação clínica em Portugal.

keywords

Curricular Internship, Clinical Research, Regulatory Affairs, Pharmacovigilance, Guidelines, Study Coordination, Legislation

abstract

This report was elaborated as part of the Master in Clinical Research Management, held between October 2020 and April 2021.This report begins by fitting the field of regulatory affairs and pharmacovigilance into the context of clinical research, as well as to detail the activities undertaken during the curricular internship at BlueClinical. During the period of training, it was possible to perform tasks inherent to the different activities undertaken by Regulatory Affairs and Pharmacovigilance team. Besides this, there was also the opportunity to perform activities related to the position of Clinical Studies Coordinator at the Centro Hospitalar do Baixo Vouga. All above allowed the acquisition of practical knowledge regarding the field of Clinical Research in Portugal.

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Abbreviations

CRO - Contract Research Organization

R&D - Research & Development

CRP - Clinical Research Partnership

ICH - International Council for Harmonisation

GCP - Good Clinical Practice

MD - Medical Devices

SUSAR - Suspected Unexpected Serious Adverse Reactions

INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P. (National Authority for Medicines and Health Products)

CEIC - Comissão de Ética para a Investigação Clínica (Ethics Committee for Clinical Research)

RNEC – Registo Nacional de Estudos Clínicos (National Register of Clinical Studies)

DSUR - Development Safety Update Report

EVCTM - EudraVigilance Clinical Trial Module

EMA - European Medicines Agency

ADR – Adverse Drug Reaction

Post-MA – Post Marketing Authorisation

GVP - Good Practices of Pharmacovigilance

PSMF - Pharmacovigilance System Master File

MAH – Marketing Authorization Holder

MLM - Medical Literature Monitoring

PSUR - Periodic Safety Update Reports

ICSR – Individual Case Safety Report

EV - EudraVigilance

EVPM – Eudravigilance Post-authorisation module

PRAC - Pharmacovigilance Risk Assessment Committee

PSUSA - Periodic Safety Update Report Single Assessments

FDA – Food and Drug Administration

USA - United States of America

EudraCT – European Union Drug Regulating Authorities Clinical Trials Database

PI - Principal Investigator

PM - Project Manager

TMF - Trial Master File

SmPC - Summary of Product Characteristics

AEMPS - Agencia Española de Medicamentos y Productos Sanitarios

CIMA - Centro de Información Online de Medicamentos de la AEMPS

SDEA - Safety Data Exchange Agreement

SOP – Standard Operating Procedure

eAF - Electronic Application Form

CRF - Case report form

SC - Study Coordinator

RA&PHV - Regulatory Affairs and Pharmacovigilance

EEA - European Economic Area

EU – European Union

ALCOA+C - Attributable, Legible, Contemporaneous, Original, Accurate and Complete

1. Introduction

This report was written within the scope of a curricular internship that was part of the Master's Degree in Clinical Research Management.

The current report begins with a literature revision regarding the fields of regulatory affairs and pharmacovigilance related to clinical trials, focusing as well on the post marketing authorization pharmacovigilance area. This topic was chosen since the intern performed the activities described further down.

This internship took place in the Portuguese company *BlueClinical – Investigação e Desenvolvimento em Saúde Lda* (BlueClinical). BlueClinical is a Contract Research Organization (CRO) which is divided into three business units: Phase I, Research & Development (R&D) and Clinical Research Partnership (CRP). Each business unit has a mission as follows:

Phase I: To conduct phase I clinical studies in healthy subjects and selected populations of patients.

R&D: To provide consultancy services in drug clinical development and act as a full-service CRO for clinical studies in patients, with special focus on early phase studies.

CRP: To support operationally the clinical research activity in partner health institutions, promoting its development, efficiency, and excellence.

Thus, this report is the result of five months of curricular internship in Regulatory Affairs and Pharmacovigilance Department (from the 6th October 2020 to the 1st March 2021), which allowed the intern to acquire competences such as regulatory expertise, clinical studies submission to Competent Authorities and other essential skills for the position of Regulatory Affairs and Pharmacovigilance Manager. The intern was also given the opportunity to start an internship in Coordination of Clinical Trials (from the 2nd March 2021 to 30th April 2021), where the intern was able to develop communication skills, to coordinate the beginning of trials in the site, to help in the monitoring visits and to follow the patient in the studies' necessary activities. In total, the intern served in the internship for about 917 hours.

In order to assess the relevance of the internship, the intern established the following goals: to identify the procedures related to the communication with the authorities; to get acquainted with the field of clinical research and pharmacovigilance by studying legislation and guidelines; to understand the applicability of the aforementioned legislation and guidelines in daily work; to develop time management, teamwork and conflict resolution

skills; to organise essential documents to clinical studies; to work with data collection software and to familiarize the self with the work environment.

This report will focus on the aspects of clinical research, present and past, and its regulatory environment. It will also go through the responsibilities of a Regulatory Affairs and Pharmacovigilance Manager and Study Coordinator (SC), and the daily related tasks.

2. State of the art - Regulatory Affairs and Pharmacovigilance in Clinical Research

In order to bring the developed activities into context, the intern conducted research focused on the early stages of clinical research and its regulatory environment, as well as on how pharmacovigilance is a crucial part of a medicine's lifecycle.

2.1. Brief history of Clinical Research

A clinical study is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product; to identify any adverse reactions to an investigational product; to study pharmacokinetic effects of an investigational product with the aim of ascertaining its safety and/or efficacy (1).

The first report of a clinical trial is recorded in the Bible and refers to the book of Daniel, where king Nebuchadnezzar ordered his young slave men to eat and drink only what the royal court used to. Daniel and his peers were allowed to follow a diet based on vegetables and water for 10 days. When this experiment ended, the enslaved men appeared appeared healthier than the others who ate the royal food diet (2).

However, the first comparative controlled trial was conducted in 1747 by a physician named James Lind. He designed a trial with the same conditions for all his patients, except for the study variables. This way, he was able to achieve a clear result – oranges and lemons are the best treatment for scurvy (2–4).

Two important aspects regarding clinical research are the blinding and the randomization of the study. The first-mentioned aspect was used for the first time within a study to investigate an extract of Penicillium to treat a common cold, where the research team and the patients were blind to the treatment. The randomization occurred for the first time in a controlled trial of streptomycin in pulmonary tuberculosis (2,5).

Another important aspect is the ethical component, for we cannot dissociate it from clinical trials. If we look throughout history, it is perceptible that the pioneer for the current ethical framework was the Hippocratic Oath. Nonetheless, this did not prevent the atrocities against humans and human experimentation. The World War II abuses were the ultimate eye-opener for the need to develop all sorts of legislation. Thus, the Nuremberg Code came into existence in 1947, where it was introduced the voluntary informed consent by the participant of the trial (2,6)

In 1962, another great step forward was taken, as the effects of thalidomide were discovered. Firstly, this medicine was released as a sedative, but it was soon used as an antiemetic for pregnant women, even though there was not enough safety information. Years later, it was confirmed the relation between Thalidomide and phocomelia, and this drug was withdrawn from the market. Following this course of events, in 1962, the Kefauver-Harris amendments were written in the United States of America (USA). These amendments required that evidence of effectiveness was to be based on well-controlled clinical trials conducted by physicians and that the study subjects would need to give informed consent (7–9)

In the requirement of clinical studies conduct, the world felt the need to have guidelines to for the protection of the human subjects participating in the clinical studies. Therefore, the Helsinki Declaration from the World Medical Association emerged in 1964 (6).

Despite all these efforts, atrocities against human life continued to happen, such as the Tuskegee study, where the participants did not receive treatment for syphilis, even after the discovery of a medicine to treat this disease, in order to study its natural evolution. Hence, in 1979, the Belmont report was created, which emphasized four basic ethical principles: autonomy, beneficence, nonmaleficence and justice (8,10).

As various countries started to draft their own guidelines, the need for harmonisation between countries emerged. If on one hand, each country was developing its own requirements, on the other hand, the pharmaceutical industry was becoming more and more international. Consequently, the industry started to feel the divergence between frameworks from country to country in such a way that it was forced to duplicate several test procedures, which were expensive and prolonged. This affected the availability of new products internationally (11,12).

As a result, the International Council for Harmonisation (ICH), which had representatives from European Union (EU), USA, Japan and pharmaceutical industries, developed the

Good Clinical Practices (GCP) guideline in 1996 known as ICH E6. To this day, this document is considered to be the universal model for the ethical conduct of clinical trials. For this reason, this guideline is constantly updating, being that the current revision is E6(R2) and the ICH committee is preparing a new revision (E6(R3)) (11,12).

2.2. Regulatory framework

In the EU, clinical trials are currently regulated by the Directive 2001/20/EC. Due to the inherent complexity of clinical trials, and to the fact that it often involves multi-centre trials in different Member States with divergent rules, it was necessary to invest in harmonisation and simplification of the administrative provisions, achieved by the establishment of transparent procedures and conducive conditions to adequate coordination of clinical trials (13,14). It should be noted that this Directive only applies to the interventional clinical studies with medicines; clinical studies with Medical Devices (MD) and non-interventional studies are not covered by this Directive. (13).

In addition, there are several guidelines published by the European Commission to support the Directive 2001/20/EC, namely:

Guideline 2010/C 82/01: “Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)”. This guidance focuses on the requests and the necessary information to submit an authorisation request, an amendment or a declaration of the end (or premature end) of clinical trials (15).

Guideline 2011/C 172/01): “Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3)”. The aim of this guideline is to address the collection, verification and reporting of adverse events and reactions that occur in a clinical trial performed in at least one EU Member State, as well as to help the management of the Suspected Unexpected Serious Adverse Reactions (SUSAR) (16).

In order to avoid the divergent interpretation of the Directive across EU countries and to minimize the administrative delays for starting a clinical study, in 2014 an EU Regulation was published: Regulation 536/2014 known as Clinical Trials Regulation. This Regulation will replace the Directive 2001/20/EC. However, currently, there is not a definitive implementation date (14,17). The main differences between the current Directive and the new Regulation are the creation of a single submission portal and the obligation for all the concerned Member States to submit a single dossier through the mentioned portal(17).

In Portugal, the Clinical Research Law (Law No. 21/2014, amended by Law No. 73/2015) is based in the Directive 2001/20/CE, regarding the interventional clinical studies with medicines. Besides this, the Clinical Research Law also addresses information about interventional clinical studies with MD, cosmetics and hygiene products, and non-interventional studies. However, when the Regulation No. 536/2014 enters into force, a portion of the prior mentioned law will be revoked, *id est* the section related to the interventional clinical studies with medicines (18,19).

The Portuguese Competent Authority for clinical trials is *Autoridade Nacional do Medicamento e Produtos de Saúde, I. P.*, (INFARMED*)* responsible for the authorisation and oversight of clinical trials (20). Another competent entity involved in Clinical Research *is Comissão de Ética para a Investigação Clínica* (CEIC), which is a national independent committee comprised by individuals connected to health and other fields of activity, CEIC's main goal is to ensure the protection of rights, safety and welfare of the clinical studies participants, through the emission of an ethical favourable opinion about the investigation protocols (21).

The communications with INFARMED and CEIC regarding the clinical studies are made through a national electronic platform: *Registo Nacional de Estudos Clínicos* (RNEC). These communications include the submission of clinical study request, substantial amendments, non-substantial amendments, the end-of-study communication, the submission of the Annual Progression Report, the Development Safety Update Report (DSUR) and of the Clinical Study Report (18).

With the view to complement the EC guidance of clinical trials, both INFARMED and CEIC developed national documents to define the required documentation and to give specific instructions (22–24).

2.3. Pharmacovigilance

There is no such thing as a risk-free medicine. Therefore, it is necessary to evaluate whether the benefits outweigh the potential harms of a certain medicine, during its life cycle. This assessment aims at guaranteeing the patients' safety and improved health conditions. In layman's terms, this is Pharmacovigilance (25).

There are some key concepts regarding Pharmacovigilance. Two of them are the adverse events and the adverse reactions. An event is related to medical occurrence in a clinical trial subject but does not necessarily have a causal relationship with the treatment, whereas a reaction consists of a direct unwanted response to an investigational medicinal product.

Both of the prior can be considered serious if, at any dose, they result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, or in a congenital anomaly or birth defect (16).

In clinical trials in the EU, the responsibility of reporting and monitoring aspects related to the safety of the product undergoing investigation relies upon the investigator and upon the sponsor. On the one hand, the investigator must report the adverse events, either serious or non-serious, as well as certain laboratory abnormalities, to the sponsor. On the other hand, the sponsor is responsible for: recording said adverse events; reporting the SUSAR's as an Individual Case Safety Report (ICSR) through EudraVigilance Clinical Trial Module (EVCTM) to the national competent authority and by e-mail to Portuguese Ethics Committee (CEIC); informing the investigators about the products' safety-related issues; the annual reporting of the DSUR to the national competent authority and the Ethics Committee, by RNEC (16,26,27).

When the investigator gains knowledge of the occurrence of a serious adverse event occurrence, he must report it within the following 24 hours. In other cases, the investigator must report the occurrence within the adequate time frame, as stated in the protocol or in the Investigator's Brochure. After knowing about such cases, the sponsor must take the appropriate measures to address potential new risks in a clinical trial. Furthermore, the sponsor must report to the EVCTM all relevant information about fatal or life-threatening suspected serious unexpected adverse reactions within 7 days after gaining knowledge about such occurrences. If the SUSAR's are not considered to be as the latter ones, they should be reported as soon as possible, but within a maximum of 15 days of first knowledge by the sponsor (16).

The EVCTM, one of EudraVigilance's modules, was developed to simplify workflow and to avert duplicate reports of SUSAR's, particularly in the case of multicentre trials. It also contributes to the facilitation of communication of said SUSAR's between national competent authorities and the European Medicines Agency (EMA) (16).

According to the 2020 Annual Report on EudraVigilance (EV), the EV received a total of 18,655,237 suspected adverse drug reaction (ADR) reports from clinical trials, being that 1,423,432 of these belong to the EVCTM (28).

The count of ADR reported by the sponsors is greater than the count reported by the National Competent Authorities, showing that the sponsors are fulfilling their responsibility and that EV is achieving its goal (Table 1) (28).

Table 1. Number of ADR reports transmitted by sponsors and National Competent Authorities to EVCTM in 2020

Source	EV Module	Transmission Type	Count
Sponsor	EVCTM	SUSAR	106 649
National Competent Authorities			7 529

Despite the fact that pharmacovigilance starts within clinical trials, it acquires greater importance afterward, when the product undergoing investigation is approved and starts to be commercialised (Figure 1).

This stage is known as the post-authorisation of introduction in the market (Post-MA).

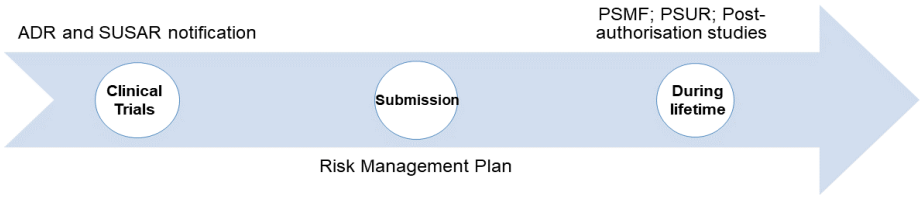

Figure 1. Pharmacovigilance in the lifetime of the medicine

In order to aid the legal requirements and to facilitate the conduct of the pharmacovigilance activities in the EU, the good pharmacovigilance practices (GVP) were created. These apply to all medicinal products authorised in the EU, whether centrally or nationally authorised (29).

The GVP are subdivided in different modules (I-X,XV-XVI), in which the developing activities in pharmacovigilance are detailed. For instance, the module II provides detailed direction regarding the requisites for the Pharmacovigilance System Master File (PSMF) - a legal requirement for the Marketing Authorization Holder (MAH) that should be located either at the site in the EU where the main pharmacovigilance activities of the MAH take place or at the site in the EU where the qualified person responsible for pharmacovigilance operates -

including its maintenance, content and associated submissions to competent authorities (30).

Another important module for the guidance of pharmacovigilance-related activities is the module VI, in which the key principles regarding the collection, recording and submission of individual reports of suspected adverse reactions associated with medicinal products for human use are depicted. This collection can be achieved through: the spontaneous report by a healthcare professional, or consumer, to a competent authority or to the MAH; reports of suspected adverse reactions from the medical literature, being that the MAH must ensure the constant monitoring of databases which contain scientific publications, as well as of local scientific journals from places where such products were authorised and are being commercialised; information on suspected adverse reactions not only from the internet or digital media but also from clinical trials, non-interventional studies, registries and post-approval studies. For serious events, the submission should take place within the 15 days that follow the day 0, that is, after taking notice of a valid case. For non-serious cases, it should happen within the 90 days that follow the day 0, through EV. It should be noted that a valid case is any case that fulfils the 4 following criteria: having someone who reports the case, someone who is able to be identified, a suspected product and a suspected adverse reaction. Furthermore, this module also mentions special situations, such as the use of medicines in pregnancy, overdose, etc., which deserve special attention (31).

Although monitoring the medical literature on their medicines is a responsibility of the MAH, the EMA provides a Medical Literature Monitoring (MLM) and Pharmacovigilance obligations reports service, due to the increased number of currently commercialised substances. This service aims at reducing duplicated information, whilst increasing the data quality and improving the safety of the medicines. This service is placed in the EudraVigilance Web Reporting Tool (EVWEB) which is part of Eudravigilance Post-authorisation module (EVPM), a platform that allows the submission and download of ICSR. In the ICSR download screen, it is possible for users to download ICSRs in bulk either from the MLM Service, to fulfil pharmacovigilance obligations (also known as L2A), or to request case narratives in the context of signal management (L2B). The L's refer to the access levels according to the Access Policy in EVWEB, being that L1 represents the access to the fewer information possible, whereas L3 represents full access (which differs from authorities to MAH) (32–34).

The GVPs also contain an entire module (VII) dedicated to the Periodic Safety Update Reports (PSUR) and other to the Signal Management. Signal Management consists in

managing information from one or multiple sources which suggests a new potentially causal association or a new aspect of a known association between an intervention and an event, either adverse or beneficial, that is considered to be likely enough to justify a verification action (35). PSUR is a report that describes the risk-benefit analysis of the medical product in a comprehensive, critical and concise way, taking into consideration either new or emerging information in the context of cumulative information on risks and benefits (36).

In conclusion, pharmacovigilance is a highly important subject, either regarding clinical trials or post-MA. Thus, it is constantly updating, without neglecting its importance towards public health.

Table 2. Main differences between pharmacovigilance during clinical research and post-MA

	Clinical Research	*Post-MA*
Phases	I	IV
	II	Post Approval studies
	III	Spontaneous Report
Main Activities	Report of SUSAR	Signal Management
	Report of Adverse Events	ICSR Reporting
	Report of Serious Adverse Events	Periodic Safety Reports
		Maintenance of PSMF
EV Module	EVCTM	EVPM

3. Internship activities

During the internship, the intern was able to go through the following areas: Regulatory Affairs, responsible for ensuring that all legal and regulatory requirements are met; Pharmacovigilance, responsible for monitoring and implementing measures which prevent adverse effects caused by pharmaceutical products; Coordination of studies, responsible for overseeing and coordinating the research process, from inception to completion.

In order to be able to accomplish the tasks, there were training sessions in matter such as: the company's Standard Operating Procedures (SOP), GCP, IATA Dangerous Goods Regulations (IATA DGR), Security Awareness in the internet and Case Report Forms (CRF) such as Medidata Rave (certificates in annex).

There are various activities associated with these fields, some of which were performed during the course of this internship (Table 3).

Table 3.List of activities developed during the internship

	OCT	NOV	DEC	JAN	FEB	MAR	APR
Legislation search	x	x	x	x	x		
Clinical trials communications			x				
Summary of Product Characteristics update's search	x	x	x	x	x		
Medical Literature Monitoring	x	x	x	x	x		
Pharmacovigilance obligations reports	x	x	x	x	x		
National and International Literature		x	x	x	x		
Safety Data Exchange Agreements				x	x		
Extended EudraVigilance medicinal product dictionary				x			
Individual Case Safety Report submission				x			
Safety Variations			x	x	x		
Feasibility Assessments							x
Preparation of essential documentation						x	
Site Initiation Visits						x	
Patient Visits						x	x
Case report form completion						x	x
Sample management						x	x
Management of the participants' expenses						x	x
Monitoring visits						x	x

3.1. Legislation search

Either in Regulatory Affairs or in Pharmacovigilance, it is crucial the weekly and monthly legislation search, given that it is necessary that the person responsible for Regulatory Affairs and Pharmacovigilance stays updated about any new or revoked guideline or legislation (Figure 2).

For those responsible for Pharmacovigilance, there is also the need to know if there are any Pharmacovigilance Risk Assessment Committee (PRAC) recommendations, European Union Reference Dates lists or Periodic Safety Update Report Single Assessments (PSUSA).

This search starts by defining the sources to be used and the covered period of time. To prevent missing information, it is imperative that the search covers entirely the period of time previously established, for instance, from Monday to Sunday of the previous week.

Furthermore, it is necessary that the outcome of this search is documented in a proper location, and if any important information is found, it must be stored and shared with the team and with the remaining interested parties, such as the client.

This task was undertaken weekly and monthly, depending on which accessed platform. The sources used were the websites of the following entities: Diário da República, INFARMED, CEIC, Heads of Medicines Agencies from Co-ordination Group for Mutual Recognition and Decentralised procedures – Human, Access to European Union law (EUR-Lex), Food and Drug Administration (FDA).

Besides the usual weekly and monthly research, whenever it is necessary or requested, the team researches the subject which the client wants regulatory clarification.

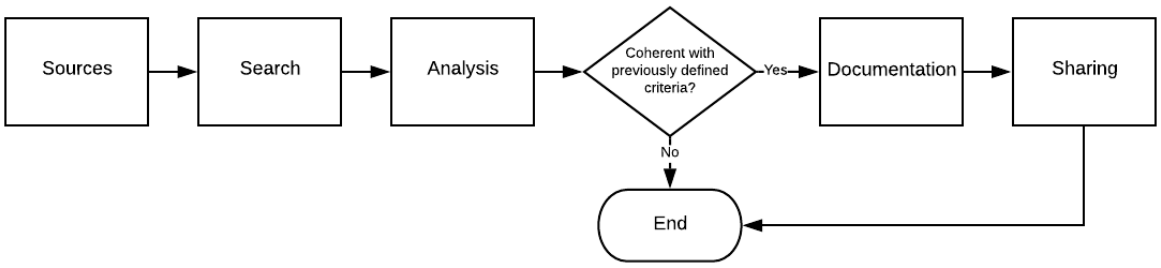

Figure 2. Flowchart regarding legislation search

3.2. Clinical trials communications

3.2.1. Notification of trial initiation

After clinical trial approval, the Sponsor of the clinical trial has to notify the Ethics Committee (CEIC in Portugal) about the clinical trial initiation (Figure 3).

In order to notify the trial initiation to the CEIC, a cover-letter should be written in Portuguese containing trial identification (protocol title, protocol code, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) number, CEIC's code and the date of trial initiation. After cover-letter signing, it should be submitted through RNEC.

After notification, the Principal Investigator (PI) and the Project Manager (PM) are informed about the communication by email. Additionally, the cover-letter should also be archived in the Trial Master File (TMF).

3.2.2. Non-substantial amendment notification

The non-substantial amendments do not require prior approval, therefore there is no timeframe to notify those type of amendments to CEIC and INFARMED. For the clinical trials of short duration (e.g. less than a year) the non-substantial amendments are submitted at the end of study.

In order to notify the non-substantial amendments a cover-letter should be written in Portuguese for CEIC and in English or Portuguese to INFARMED. In the cover-letter all the modified documents should be listed, alongside a brief justification for any change. The new version of the documents should be sent as attached with the cover-letter (a version with tracked changes and a clean version should be sent). After cover-letter signing, it should be submitted through RNEC.

After notification, the PI and the PM are informed about the communication by email. Additionally, the cover-letter should also be archived in the TMF.

3.2.3. End of study notification

Within 90 days after the clinical trial conclusion, the end-of-study has to be notified to CEIC and INFARMED (Figure 3).

In order to notify the end-of-study a cover-letter should be written in Portuguese for CEIC and in English or Portuguese to INFARMED. Additionally, a specific form of end-of-study should be completed and sent attached with of the cover-letter. After cover-letter and form signing, they should be submitted through RNEC.

After notification, the PI and the PM are informed about the communication by email. Additionally, the cover-letter should also be sent to be archived in the TMF.

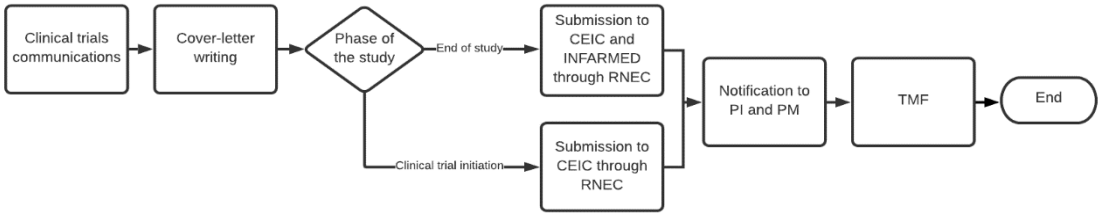

Figure 3. Flowchart regarding clinical trials communications

3.3. Clinical trial Pharmacovigilance

3.3.1. Summary of Product Characteristics update's search

In a clinical trial for a medicine already approved and available in the market, and for a medical indication already approved, the Reference Safety Information should be the Summary of Product Characteristics (SmPC). To ensure the participant's safety, the latest version of the SmPC should be considered. Therefore, it is required to monitor the published version of the SmPC (Figure 4).

To accomplish this, on a weekly basis the websites of the entities which had approved the medicines are consulted to verify if a new version of the applicable SmPC was published. If a new version of the SmPC is found, the text of the old version is compared with the new version. In case there are medical changes, the new version of the SmPC is sent to a Medical Manager who will assess whether the changes have an impact in the trial conduct. If so, a substantial amendment should be submitted, if not a non-substantial amendment, respectively.

During the internship, this task was performed weekly through platforms of INFARMED, EMA, FDA and Centro de Información Online de Medicamentos de la AEMPS (CIMA).

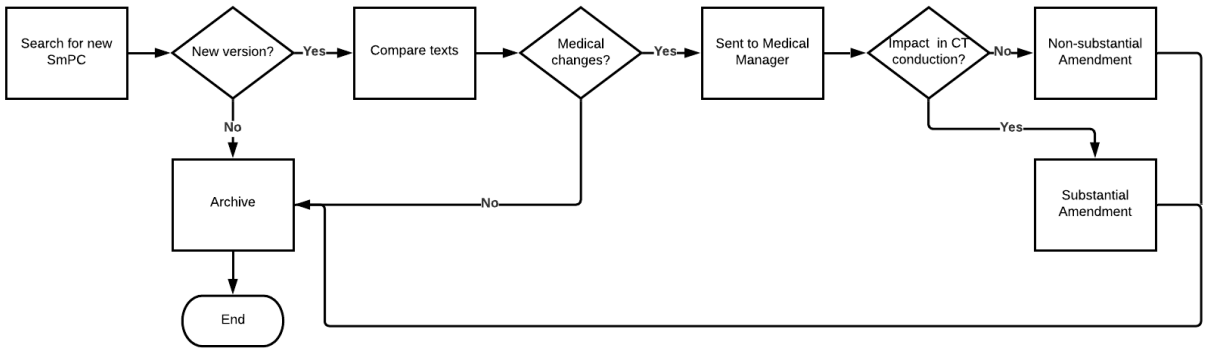

Figure 4. Flowchart regarding SmPC update's search

3.4. Post-MA Pharmacovigilance

3.4.1. Medical Literature Monitoring & Pharmacovigilance Obligations

One of the activities described in the GVP module VI is the attainment of the MLM and the entry of relevant information into the EV database by the EMA, as well as the pharmacovigilance obligations reports, which is a partially restricted access to ICSRs sent by other organisations where they concern suspect drugs for which they hold Marketing Authorisation (33).

To accomplish this activity, it is required an EV account, in order to login in the platform where it is possible to use research criteria - which must be elaborated considering the substances involved in the pharmacovigilance monitoring. This research must be done comprising the whole period of time, which in this case was weekly and with two weeks of delay, to ensure that all the results are properly monitored (Figure 5).

After downloading the ICSR, each result should be individually analysed, their relevance assessed and the inclusion or non-inclusion in the internal database justified.

These cases are inserted into the internal database, which is crucial to help with the signal detection-information on a new or known adverse event that may be caused by a medicine and requires further investigation-as well as with the elaboration of a PSUR.

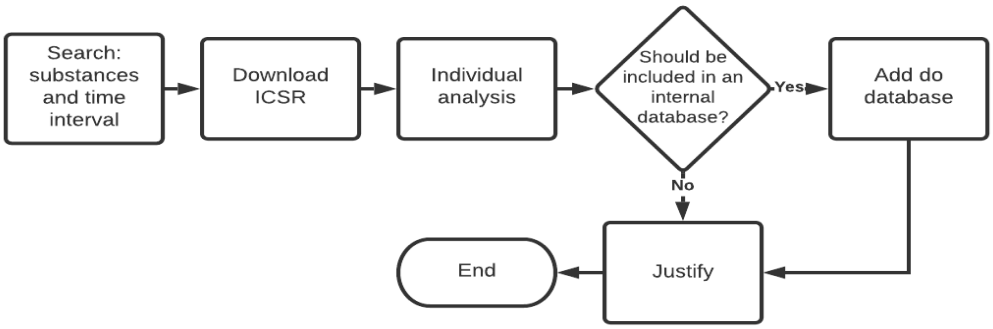

Figure 5. Flowchart regarding MLM and Pharmacovigilance obligations

3.4.2. National and International Literature

Medical literature is one of the possible sources for a safety data report about a medicine. Thus, it is necessary that it goes under monitoring.

Being so, a pharmacovigilance manager is responsible to ensure that the information about its medicines is regularly monitored.

The repositories of articles should be chosen such as PubMed and assessing which search terms comprise more accurately the information intended to monitor (e.g. the name of the active substance and words like pregnancy, breastfeeding, overdose, misuse). Once the research criteria are settled, the results should be assessed weekly - covering the whole period of one week. This is achieved by reading firstly the title and the abstract of the article. If the title and the abstract contain any information of special interest, the whole article must be read. If the article contains safety information, it should be archived in the team's database. However, if the article describes a valid or plausibly valid case - this is, following the four criteria of notification: identifiable subject, identifiable reporter, at least one suspected adverse reaction and at least one suspected medicine - it is necessary to comply with the submission timelines.

Besides searching within international literature, it is also necessary to conduct research in scientific journals considering the therapeutic indications of the products commercialised by the MAH. One example of this search in the *Revista Sinapse* for products which involve the nervous system.

To clarify the literature research process and its implications, a flowchart was elaborated (Figure 6).

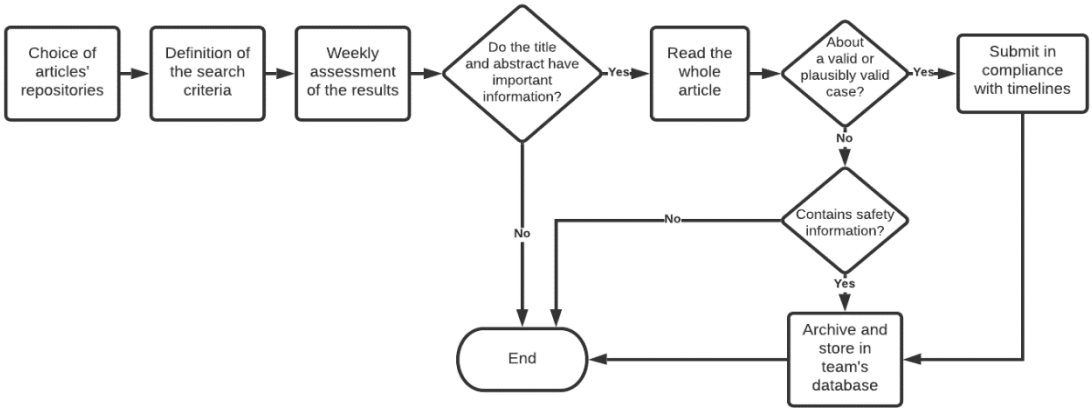

Figure 6. Flowchart regarding National and International Literature

3.4.3. Safety Data Exchange Agreements

According to the GVP module VI (V1.B.7), it is necessary to establish of a pharmacovigilance agreement when there is shared safety information and/or shared pharmacovigilance responsibilities between two companies.

The manufacturers - who can be batch releasers, the distributors outside of the EU - lay within this framework, since they do not follow the same EU legislation. In the same way, companies following a decentralised procedure and companies of mutual-recognition procedure are also comprehended in this framework.

This task was undertaken whenever a partner MAH requested it. When our client was the MAH of the product, the SDEA was set into motion by our team, following the SOP established for the accomplishment of this task.

3.4.4. Extended EudraVigilance medicinal product dictionary

Whenever a new product with a MA is approved in the European Economic Area (EEA), or whenever variations related to the data of products already with a MA are approved, it is necessary to proceed to the electronic submission of information on medicinal products for human use using the extended EudraVigilance Medicinal Product Report (Figure 7).

This way, whenever the team receives an alert stating that a new product received a MA, the team prepares a support document to the data submission of this new product through EV. After going through quality control (QC), the submission through the EV portal regarding the Extended EudraVigilance medicinal product dictionary is undertaken by the person

assigned to the task. This submission has within it all the information previously written in the support document. After the submission, the team must wait for the acknowledgement code sent by EV.

Furthermore, whenever the team receives an alert stating that some of the previously submitted information was modified, the person assigned to the task updates the information in the EV portal. After the update, the team must wait for the acknowledgement code sent by EV.

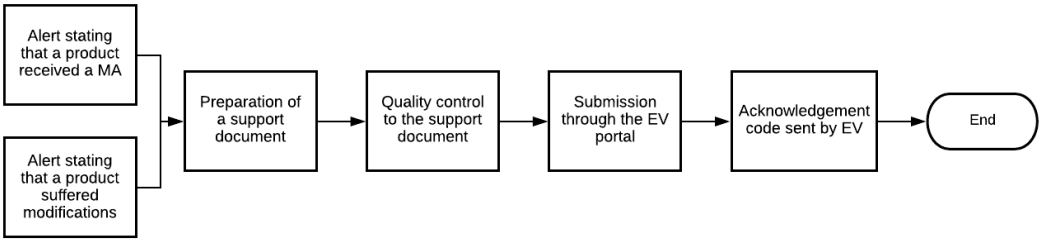

Figure 7. Flowchart regarding Extended EudraVigilance medicinal product dictionary

3.4.5. Individual Case Safety Reports submission

One of the responsibilities of a MAH is monitoring of the weekly search of medical literature in a wide range of databases and scientific journals (Figure 8).

As soon as it is found, in one of these sources, an article that meet the four criteria of notification - identifiable subject, identifiable reporter, at least one suspected adverse reaction and at least one suspected medicine - it should be sent to the medical manager. Then the medical manager should assess the causality and severity and should refer to which non-documented clinical information is necessary to be known about the article in question.

After assessment of case seriousness, it is necessary to comply with the legal timelines for its submission to the authorities. For serious events - the submission should take place within the 15 days that follow the day 0 and for non-serious cases, it should happen within the 90 days.

The author of the article should also be contacted in order try to know whether the mentioned product is from the MAH in question and to obtain more information that might be necessary to the case's notification to the authorities.

The ICSR form must be filled either having all the necessary information and the confirmation that the product in question is from the MAH or not knowing which is the commercial name of said product. This form, before it is submitted in the EV, goes through QC, this being undertaken by one of the members of the team who was not responsible for its elaboration.

After submitting in the EV, it is necessary ensure that a notification of successful submission is received.

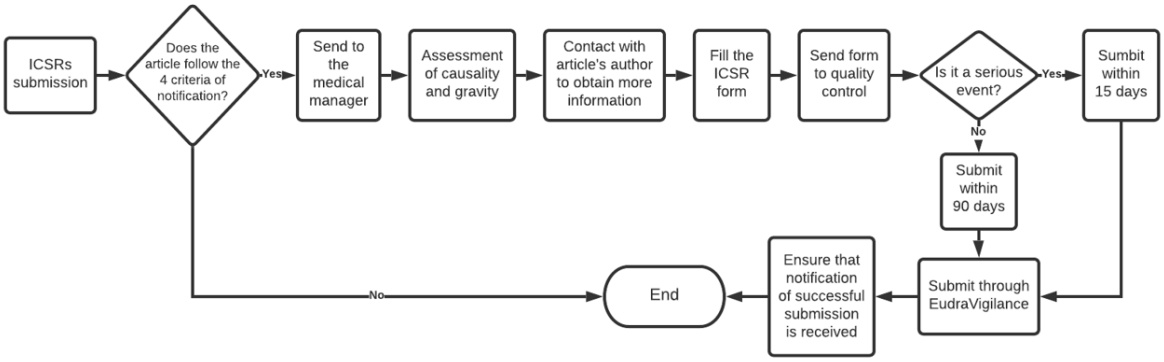

Figure 8. Flowchart regarding Individual Case Safety Reports submission

3.4.6. Safety Variations

Safety variations can emerge after the evaluation undertaken by the PRAC or by the PSUSA, of the SmPC texts, the information brochure or the primary and/or secondary packaging of a certain medicine (Figure 9)

This task followed the SOPs previously defined. If there were published new PRAC recommendations or PSURs evaluations which could have impact in the products under the responsibility of the pharmacovigilance team in the legislation research, the team is notified by email.

After one member of the team is appointed to be the person responsible for managing MA variations, all the data necessary should be gathered and the documents to be submitted to the competent authorities must be elaborated along with the texts affected by the variations.

The person appointed then makes the modifications proposed by the authority and assesses which type of variation (types IA, IAin, IB or II) was implemented, which depends

on the impact those variations have in the to-be-modified texts. This person also fulfils the electronic application form (eAF) and the cover letter.

During the internship, the pharmacovigilance team was not the responsible for the variations' submission. However, it was one of their responsibilities to prepare all the necessary documents for submission.

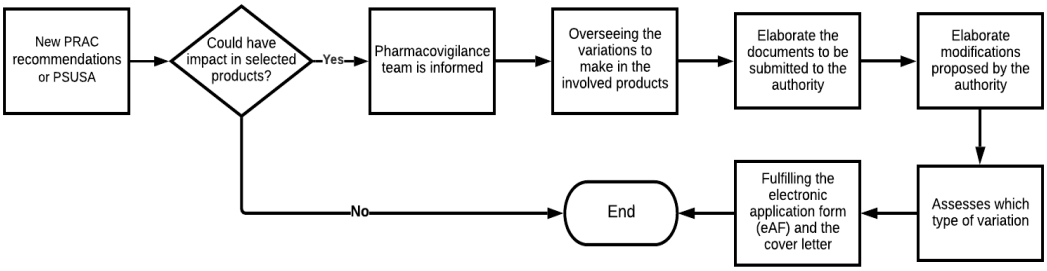

Figure 9. Flowchart regarding Safety Variations

3.5. Coordination of studies

3.5.1. Feasibility Assessments

One of the possible activities that can be undertaken by a SC is helping the PI during the Study Feasibility Assessments, whenever the PI requires assistance. During these visits, that can be either in person or remotely, the SC helps the PI by filling the inquiries related to: the available human resources; the facilities and equipment necessary during the study; the number of patients the hospital receives who have the pathology of interest; the manner through which the samples are processed. Besides gathering with the PI, in in-person visits the sponsor representative also visits the facilities. After the visit, the SC and the PI are notified on whether the study will or will not be conducted in the site.

3.5.2. Preparation of essential documentation

After choosing which site will be used to conduct the study, it is necessary to prepare certain documents which are essential to the study's submission to the authorities, such as the declaration of the site's conditions and the declaration of the medicine's path. The responsibility for the preparation of said documents lies upon the site itself, being that, for most of the times, the SC helps the PI in said preparation, so that all documents are written according to the requisites asked by the sponsor.

3.5.3. Site Initiation Visits

The Site Initiation Visits of a study are undertaken after the site in which the study will take place is selected, and after the approval from INFARMED and CEIC. In these visits, the protocol is recalled, and people are taught how to operate with certain equipment that will be used afterwards. The team also receives training regarding the procedures that will be implemented.

The role of the SC is to streamline of scheduling the visit, by contacting the investigation team, to ascertain its availability. The SC is also responsible for keeping in touch with the monitor and for organising all the documents necessary to the beginning of the study, as well as for ensuring that documents such as the Delegation Log and the Training Log are appropriately signed.

Briefly, these two documents prove that the team member received training in all the protocol's requirements (training log) and is properly delegated by the PI to the task (delegation log).

3.5.4. Patient Visits

The patient visits of the patients occur during the study plan described in the study protocol.

The SC prepares the visit: scheduling the exams foreseen by the protocol, preparing working sheets so that all required information is collected in each visit according to protocol, reminding the participants about the scheduled visits. Whenever it is necessary, the SC accompanies the patient during their visit to the site, aiding in the necessary procedures to be undertaken during said visit and according to the protocol.

3.5.5. Case report form completion

A crucial activity in clinical studies after patient visits is the appropriate data-entry in the CRF with the data from the source documents. These documents may be clinical diaries, nursing sheets or exams undertaken by the participant. The CRF filling must be accomplished in a way that all data is attributable, legible, contemporaneous, original, accurate and complete (ALCOA+C).

This task can be accomplished by a SC when delegated by the PI, being noted that the ultimate responsible for the inserted data remains the PI.

3.5.6. Sample management

A great deal of clinical studies needs specific kits to harvest biological samples from patients (Figure 10).

These kits are supplied by the sponsor. Most of the time, these kits include harvest tubes, pregnancy tests and drug-detecting chemicals, which are under a very strict expiration date. This date must be regularly checked, so that the kit is always used in optimal condition. Besides checking the expiration date, the SC also manages the kits' stock, so that every visit scheduled according to the study protocol is never missing any supplies. When in possession of the required competences, the SC can also participate in the processing of the biological samples, so that they can be sent afterwards to the central laboratory, where they will be analysed.

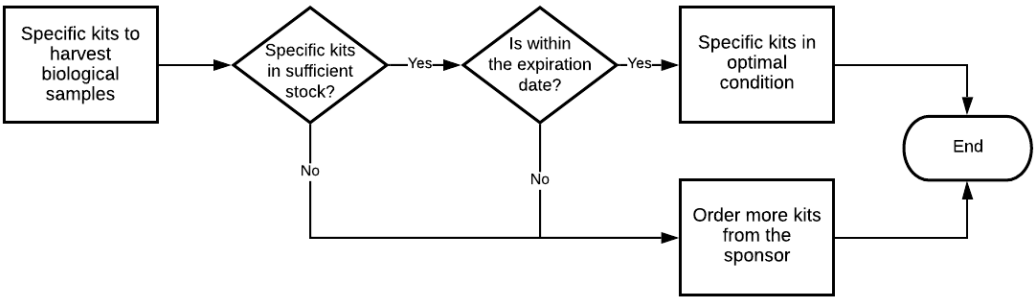

Figure 10. Flowchart regarding Specific Kits Management

3.5.7. Management of the participants' expenses

Another possible task that can be undertaken by the SC is the management of the participants' payments. Usually, the SC acts as a bridge between the patient, the sponsor and the financial services of the hospital. The SC is responsible for making sure that the receipts regarding food and commute expenses are anonymised, as well as for sending them to the sponsor (either through the monitor or through a platform given by the sponsor) and to the financial services of the hospital (Figure 11).

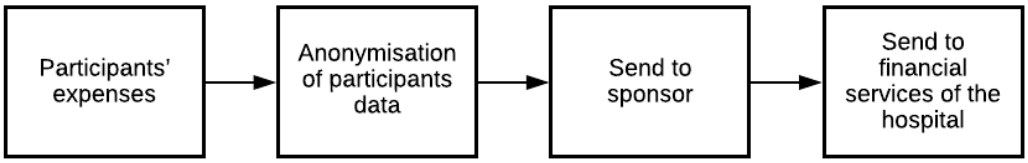

Figure 11. Flowchart regarding management of the participants' expenses

3.5.8. Monitoring visits

One of the activities of a SC is to aid in the monitoring visits, carried by the Sponsor or CRO of the study, at the site. These visits can be either remote - the monitor arranges a phone call or a video call to review pending matters and to help in missing aspects - or presential - where the monitor, besides reviewing the Investigator Site File and the patients' dossiers, might also give training to the team or talk to the PI about the site's recruitment state and sometimes about meetings.

This task was always accomplished in coordination with the studies' monitors and according to the protocol.

The previously described activities were accomplished within the clinical studies enumerated in Table 4.

Table 4. Clinical studies attended during internship

Study Code (EudraCT number)	Therapeutic area and study phase
Z7224L02 (2016-004558-13)	Non Cystic Fibrosis Bronchiectasis / Phase III
EFC16723 (2020-003117-35)	Chronic rhinosinusitis without nasal polyposis / Phase IIb
NN9535-4352 (2017-003619-20)	Diabetic Retinopathy in Subjects With Type 2 Diabetes / Phase III
EFC15805 (2018-001954-91)	Chronic obstructive pulmonary disease / Phase III
LPS16677 (2020-001217-20)	Uncontrolled persistent asthma / Phase IV
B5091007 (2016-003866-14)	Clostridium difficile infection / Phase III
747-303 (2015-002560-16)	Nonalcoholic Steatohepatitis / Phase III
20170625 (2018-004565-14)	Dyslipidemia

4. Critical discussion of acquired skills and their impact on the national context of Clinical Research

Clinical research is composed of a wide range of fields. Thus, it is necessary the existence of a multidisciplinary team in the backstage, in order to ensure that everything happens in the best way possible, and that the participants' safety is always the first priority.

This team includes the regulatory affairs and pharmacovigilance (RA&PHV) managers, who are responsible for ensuring the participants' safety in clinical studies, either through regulatory information search to make sure that the studies are being conducted in a way that protects the participants' rights, or through the reporting of safety information to the competent authorities, who shall take the appropriate measures.

One of the functions of a regulatory affairs and pharmacovigilance manager the understanding of the guidelines and the legislation, as well as how to apply them. In this internship, it was possible to understand practically the GVP and the GCP, as well as the 2001/20/EC directive and its auxiliary documents. This competence is crucial in the world of clinical investigation because, for Portugal to be recognised as advantageous country to invest in, it is necessary the existence of capable and competent teams.

As a RA manager, the intern was able to get involved in the communications with INFARMED and with CEIC and to understand sponsor´s obligations towards the authorities - studies' submission, initiation and end of studies' communications and non-substantial amendments notification. The intern was also able to understand how to use the RNEC platform from the sponsor's perspective, as well as how to address these entities.

In this internship, the intern was also given the opportunity to get acquainted with the post-MA perspective of medicines, in the PHV area as well as in the RA area. As a RA manager, the intern was able to elaborate all necessary documents to the submission of safety variations to the authorities. On the other hand, as a PHV manager, the intern was able to undertake crucial tasks related to monitoring of medicines, either exclusively approved or approved and commercialised. Hence, it was possible for the intern to understood that the life cycle of a medicine does not end with the end of the clinical studies and its commercialisation authorisation.

Besides a RA&PHV team, the SC are also crucial for the success of Clinical Investigation. Their responsibilities are aiding the investigation team, mainly the PI, in the conduction of the clinical study at the investigation site.

During the period of internship, the intern was given the chance to serve as an intern in the clinical studies' coordination area, in Centro Hospitalar do Baixo Vouga, where the intern was able to follow patients during their visits to the hospital and to participate in initiation and monitoring visits. Therefore, the intern was able to experience first-hand the reality of observational studies and clinical trials, in terms of patient intervention and of logistics and resources needed to implement these studies. In this field, the intern gained a better understanding of how a SC can turn a trial site, in this case located in Portugal, into a reference and an attractive place to implement clinical trials, changing the idea that has persisted for several years that Portugal is only a last resource when it comes to Clinical Investigation.

Therefore, there was space for reflection about the Strengths, Weaknesses, Opportunities and Threats (SWOT) during the course of this internship (Figure 12).

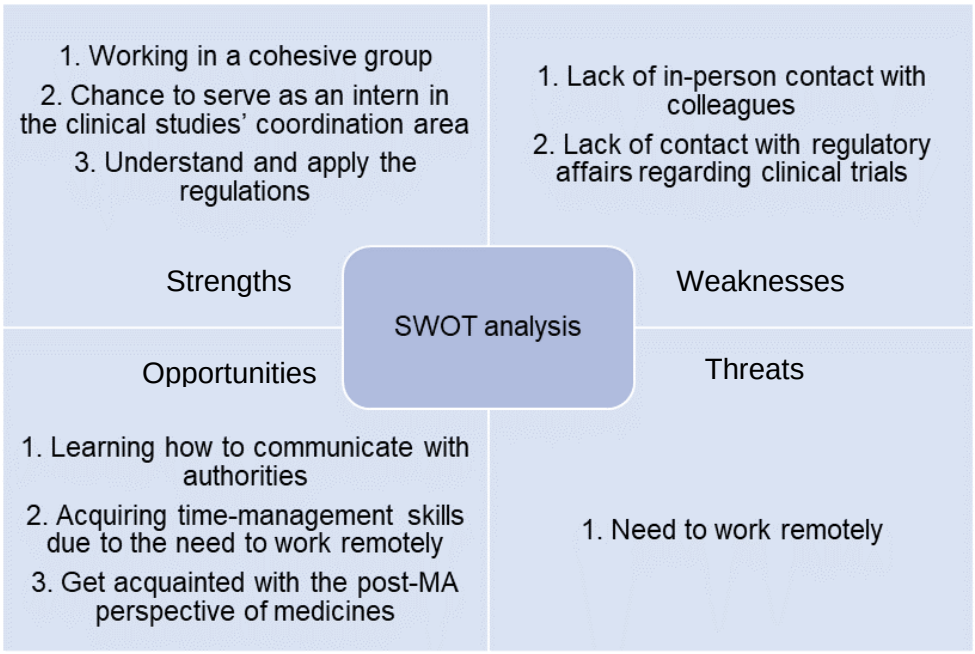

Figure 12. Analysis SWOT of the internship

Hence, the intern was able to understand that it is necessary to have a cohesive multidisciplinary team, equipped and focused in Clinical Research, to convert Portugal into a successful country regarding this field.

As can be observed in Table 5, the intern assessed the goals previously self-defined for this internship. The achieved conclusion is that, in general, the goals were accomplished. However, it is always possible to improve.

Table 5. Internship goals and their assessment

INTERNSHIP GOALS	GOALS' ASSESSMENT
Identify the procedures related with the communication with the authorities	The goal was partially achieved through the notifications of study-start, end-of-study and non-substantial amendments to INFARMED and CEIC, missing the submission of studies to INFARMED and CEIC.
Search and assessment of the legislation and guidelines found in the websites of the relevant entities to clinical investigation and pharmacovigilance	The goal was achieved through the weekly search of legislation and guidelines, its assessment and by sharing it with the interested parties.
Understand the applicability of the GVP in the daily tasks of pharmacovigilance	The goal was partially achieved through the submission of ICSR, the search of international literature and the MLM. The practical aspect of the elaboration of PSUR and Signal Management, and management of the PSMF, were not achieved.
Schedule activities according to their importance and urgency	The goal was accomplished via daily and weekly management of the designated tasks.
Develop social and working competences, such as conflict resolution and teamwork	The goal was achieved through the patient visits and by working within multidisciplinary teams.
Organise essential documents to clinical studies	The goal was achieved through the organisation of the Investigator Site File, but also by archiving all communications with partners and authorities.
Work with data collection software	The goal was accomplished through the data insertion on CRF.
Familiarize with the work environment	The goal was accomplished.

5. Conclusion

Undertaking a curricular internship is always a great opportunity to strengthen the theoretical knowledge acquired during the Master's but it is also an opportunity to gain experience and to learn new aspects of the field.

Despite the difficulties brought by the current pandemic, such as working remotely, the ability to learn was not significantly affected. In fact, teamwork and constant communication allowed the internship to be rewarding and the proposed tasks to be fulfilled.

The initially proposed activities were almost fully accomplished, but some were left undone due to the transition from Regulatory Affairs and Pharmacovigilance area to Coordination of Clinical Studies area, inside BlueClinical. The intern believes this turn of events did not represent a disadvantage, since it has allowed the intern to widen the experience in other fields.

In conclusion, the participation in the curricular internship was certainly a great asset to the intern's integration within the working environment.

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Certificate of Completion

This is to certify that

Ana Brito

Has successfully completed the on-line training module,

Good Clinical Practice:

A Refresher Course for all Site Personnel Working on Clinical Research Studies (including ICH E6, Revision 2 Changes)

Version 1.0, January 2018

on

07 Oct 2020

This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors.

Syneos Health

Certificate of Completion

This is to certify that

Ana Brito

Has successfully completed the on-line training module,

IATA Dangerous Goods Regulations
62nd Edition v21.1

on

02 Mar 2021

Ana Brito

has successfully completed the training

Security Awareness

by

wizer

10/07/2020

Certificate *of* Completion

Medidata Classic Rave EDC Essentials for Clinical Research Coordinators

Name: Ana Brito

Date of Completion: 15 Mar 2021

Application: Rave EDC and Rave Modules

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