# INTERNSHIP REPORT

# IN A CLINICAL RESEARCH UNIT

Maria Carlos Murça Elias Moreira

Internship Report submitted in partial fulfilment of the requirements for the Degree of Master in Clinical Research Management

This Master's Degree is a collaboration between Universidade de Aveiro and NOVA University Lisbon (Faculdade de Ciências Médicas | NOVA Medical School; Instituto Superior de Estatística e Gestão da Informação/NOVA IMS — Information Management School; Escola Nacional de Saúde Pública/NOVA National School of Public Health;)

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February 2021

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# Resumo

O presente relatório descreve as tarefas e atividades realizadas no âmbito da coordenação de estudos clínicos durante o estágio curricular, inserido no Mestrado em Gestão da Investigação Clínica e desenvolvido no Centro Hospitalar Universitário de Lisboa Central (CHULC).

O estágio curricular decorreu no Centro de Investigação do CHULC e teve a duração de cinco meses, tendo sido encurtado devido à pandemia por COVID-19. O principal objetivo a cumprir com a realização deste estágio foi a aplicação prática, em ambiente hospitalar, de todos os conhecimentos e ferramentas adquiridos ao longo da vertente teórica do mestrado.

Neste relatório é feito um enquadramento teórico da investigação clínica, com ênfase nos ensaios clínicos e na realidade portuguesa, bem como uma pesquisa bibliográfica no tema “Investigação Clínica em Crianças”. A descrição de tarefas e estudos seguidos ao longo do estágio, no âmbito da coordenação de ensaios clínicos, também é apresentada no relatório.

A realização deste estágio num Centro de Investigação provou ser uma experiência muito completa que permitiu ter uma visão abrangente de todo o circuito de um estudo num hospital.

**Palavras-chave:** estágio curricular, ensaios clínicos, centro de investigação, coordenadora de ensaios clínicos, pediatria

# Abstract

This report describes the tasks and activities carried out within the scope of the coordination of clinical studies during the curricular internship, inserted in the Master in Clinical Research Management and developed at the Centro Hospitalar Universitário de Lisboa Central (CHULC).

The curricular internship took place at the CHULC's Research Unit and lasted for five months, having been shortened due to the COVID-19 pandemic. The main objective to fulfil with the accomplishment of this internship was the hands-on application, in hospital environment, of all the knowledge and tools acquired along the theoretical component of the master's degree.

This report provides a theoretical framework for clinical research, with an emphasis on clinical trials and the Portuguese reality, as well as a bibliographic review on the topic "Clinical Research in Children". The description of tasks and studies followed throughout the internship, within the scope of clinical trials coordination, is also presented in the report.

The completion of this internship in a Research Unit proved to be a very complete experience that allowed for a broad view of the entire circuit of a study in a hospital.



**Keywords:** curricular internship, clinical trials, research unit, clinical research coordinator, paediatrics

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# List of abbreviations

AE - Adverse Event
APIFARMA - Associação Portuguesa da Indústria Farmacêutica
CEIC - Ethics Committee for Clinical Research (Comissão de Ética para a Investigação Clínica)
CHLC - Centro Hospitalar de Lisboa Central
CHULC - Centro Hospitalar Universitário de Lisboa Central
CIOMS - Council for International Organizations of Medical Sciences
COV - Close-Out Visit
CRA - Clinical Research Associate
CRC - Clinical Research Coordinator
CRF - Case Report Form
CRO - Contract Research Organization
CTA - Clinical Trial Agreement
CTD - Common Technical Document
CTU - Clinical Trials Unit
CV - Curriculum Vitæ
DGEEC - Direção-Geral de Estatísticas da Educação e Ciência
ESAO - Epidemiology and Statistical Analysis Office
GCP - Good Clinical Practice
GDPR - General Data Protection Regulation
HCC - Hospital de Curry Cabral
HDE - Hospital Dona Estefânia
HSAC - Hospital de Santo António dos Capuchos
HSJ - Hospital de São José
HSM - Hospital de Santa Marta
ICF - Informed Consent Form
ICH – The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP - Investigational Medicinal Product
INFARMED - National Authority of Health Medicines and Products (Autoridade Nacional do Medicamento e Produtos de Saúde I.P.)
IPCTN - Inquérito ao Potencial Científico e Tecnológico Nacional
ISF - Investigator Site File
IWRS - Interactive Web Response System
MAA - Marketing Authorization Application

MAC - Maternidade Dr. Alfredo da Costa

MEGIC - Master in Clinical Research Management

NA – Not Applicable

NMS-UNL - NOVA Medical School, Universidade Nova de Lisboa

ORSP - Office for Registry and Support of Projects

PAES - Post-Authorization Efficacy Study

PAS - Post-Authorization Study

PASS - Post-Authorization Safety Study

PI - Principal Investigator

PtCRIN - Portuguese Clinical Research Infrastructure Network

R&D - Research and Development

SAE - Serious Adverse Event

SDV - Source Data Verification

SIV - Site Initiation Visit

SOP - Standard Operating Procedure

SQV - Site Qualification Visit

TMF - Trial Master File

WHO - World Health Organization

# 1. Introduction

This report addresses the internship centred on study coordination training in a clinical setting, which is part of the master's degree in clinical research management (MEGIC) from Universidade Nova de Lisboa in association with Universidade de Aveiro.

The internship was developed in the Centro Hospitalar Universitário de Lisboa Central (CHULC), a group of six tertiary hospitals, affiliated to NOVA Medical School, Universidade Nova de Lisboa (NMS-UNL). This hospital centre is committed to develop high-quality clinical research, including clinical trials.

The internship lasted five months and took place at the Research Unit of CHULC, being supervised by the Research Unit Coordinator Luís Pereira-da-Silva, MD, PhD and co-supervised by an experienced clinical research coordinator (CRC) and GCP manager Ana Cunha, PhD.

Over the course of this internship, the aspiration was for the opportunity to apply, on the field, the knowledge and skills, as a CRC, previously acquired in the theoretical component of the MEGIC.

This curricular internship report is divided into four chapters. The first, includes the introduction, comprising the internship objectives, an overview and characterization of the host institution and a portrayal of the current clinical research and development (R&D) process, with a special emphasis on the clinical research in Portugal. This chapter also includes a brief review of literature on Clinical Research in Children. In the second chapter, a description of the main tasks performed as a CRC is provided, as well as a summary of the clinical studies followed during my internship. The acquired skills, the difficulties that had to be overcome, and whether or not the objectives set were met and any other significant occurrences are discussed in chapter three. The last chapter addresses the conclusions.

## 1.1. Internship objectives

At the beginning of the internship, with advice from the supervisors, the following objectives that reflected the expectations about the training were defined:

- To participate and be familiar with all stages of a clinical study, from the research centre's perspective, since the initial contact from the sponsor (feasibility questionnaire) to the close-out visit;

- To perform, as CRC, in diverse clinical trials and observational studies, in different medical specialties and settings;
- To improve personal skills, including teamwork, critical thinking, communication, time management, and autonomy;
- To establish a contact network with the major entities in clinical research.

## 1.2. Host Institution: Centro Hospitalar Universitário de Lisboa Central

The Centro Hospitalar de Lisboa Central (CHLC) was created on February of 2007 by the Decree-Law no. 50-A/2007 and gathered Hospital de São José (HSJ), Hospital de Santo António dos Capuchos (HSAC), Hospital de Santa Marta (HSM) and Hospital Dona Estefânia (HDE). Decree-Law no. 44/2012 included Hospital de Curry Cabral (HCC) and the Maternidade Dr. Alfredo da Costa (MAC) in CHLC. In 2018, this group of hospitals became university hospitals, linked to NMS-UNL, and is currently named Centro Hospitalar Universitário de Lisboa Central, as recognized in the Decree-Law no. 61/2018[1,2]. CHULC currently has around 1500 doctors, 2500 nurses, 700 diagnostic and therapy technicians, distributed by over 40 medical specialities and sub-specialities.

As a Clinical Research Centre, CHULC aims to provide to their investigators all the essential infrastructures required to conduct clinical research, which is centralized in its Research Unit.

### 1.2.1. Research Unit of CHULC

Mission and historical notes

The Research Unit was created to promote quality investigation, in a sustained and organized manner, in the six hospitals that compose the CHULC. It was created in 2009 and has since given support to every CHULC professional involved in clinical research, including doctors, nurses, phycologists, pharmacists and diagnostic and therapy technicians[3].

CHULC belongs to the Portuguese Clinical Research Infrastructures Network (PtCRIN) consortium, represented by the Research Unit[4]. The PtCRIN was developed primary to implement academic clinical trials and to promote cooperation in clinical research, increasing research quality and therapeutic innovation.

## Structure

The Research Unit of CHULC is composed of three functional structures: the Clinical Trials Unit, the Epidemiology and Statistical Analysis Office and the Office for Registry and Support of Projects. The Secretariat provides support to all three functional structures. A schematic representation of the organizational structure of the Research Unit's organizational structure is presented below (Figure 1)[5].

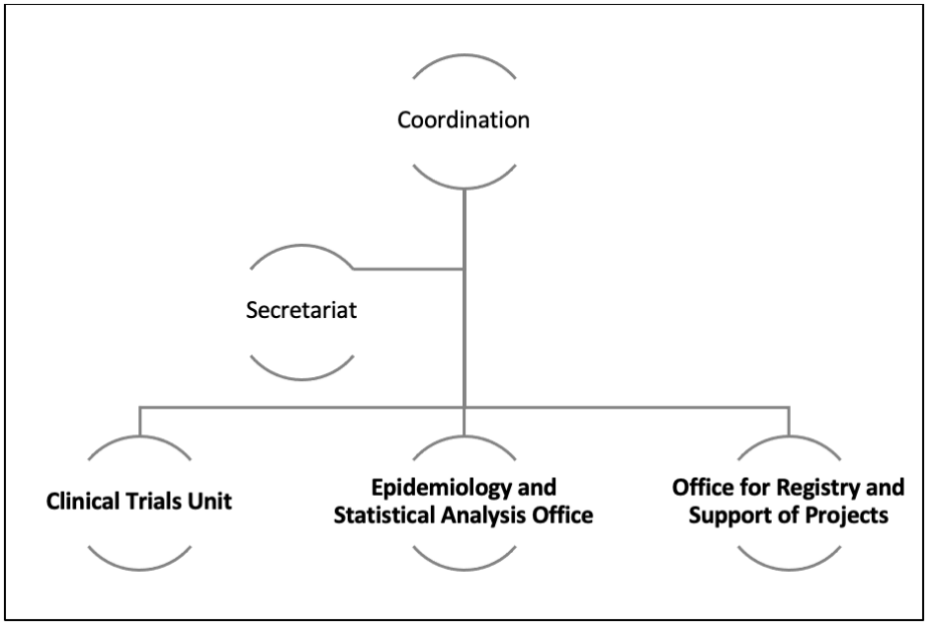


**Figure 1.** Research Unit Structure

### 1.2.1.1. Clinical Trials Unit

The Clinical Trials Unit (CTU) of the CHULC Research Unit was created in 2016, with the mission to centralize the support to sponsored clinical research, developed in the six hospitals of the CHULC, which includes clinical trials, medical device clinical studies, post-authorization efficacy studies (PAESs), post-authorization safety studies (PASSs) and other clinical studies. Currently, the CTU is coordinated by Margarida Ferreira, PharmD, MSc..

This CTU is committed to manage the entire process involved in sponsored clinical studies, which includes communication with the Sponsor/Contract Research

Organization (CRO), Research Teams, Institutional Ethics Committee, CHULC Financial Department and finally the CHULC Managing Board. An important task of the CTU is to control and avoid unjustified delays in the approval process of clinical trials/studies.

## Performance during 2019

During 2019, the CHULC received 110 feasibilities distributed by more than 31 therapeutic areas/specialties. CHULC's Managing Board approved 15 clinical trials and 12 observational studies. The average approval time for new clinical trials/studies was 20.6 days. A summary of the distribution of the approved clinical trials/studies in the 6 hospitals of CHULC by therapeutic area/ medical specialty is presented in Table 1 and Figure 2[3].

**Table 1.** Distribution of approved clinical trials/studies per hospital in 2019[3]

| Hospital / Year | Hospital Curry Cabral | Hospital Dona Estefânia | Hospital Santo António dos Capuchos | Hospital São José | Hospital de Santa Marta | Maternidade Dr. Alfredo da Costa | Total |
|---|---|---|---|---|---|---|---|
| **2019** | **6** | **4** | **9** | **1** | **5** | **2** | **27** |

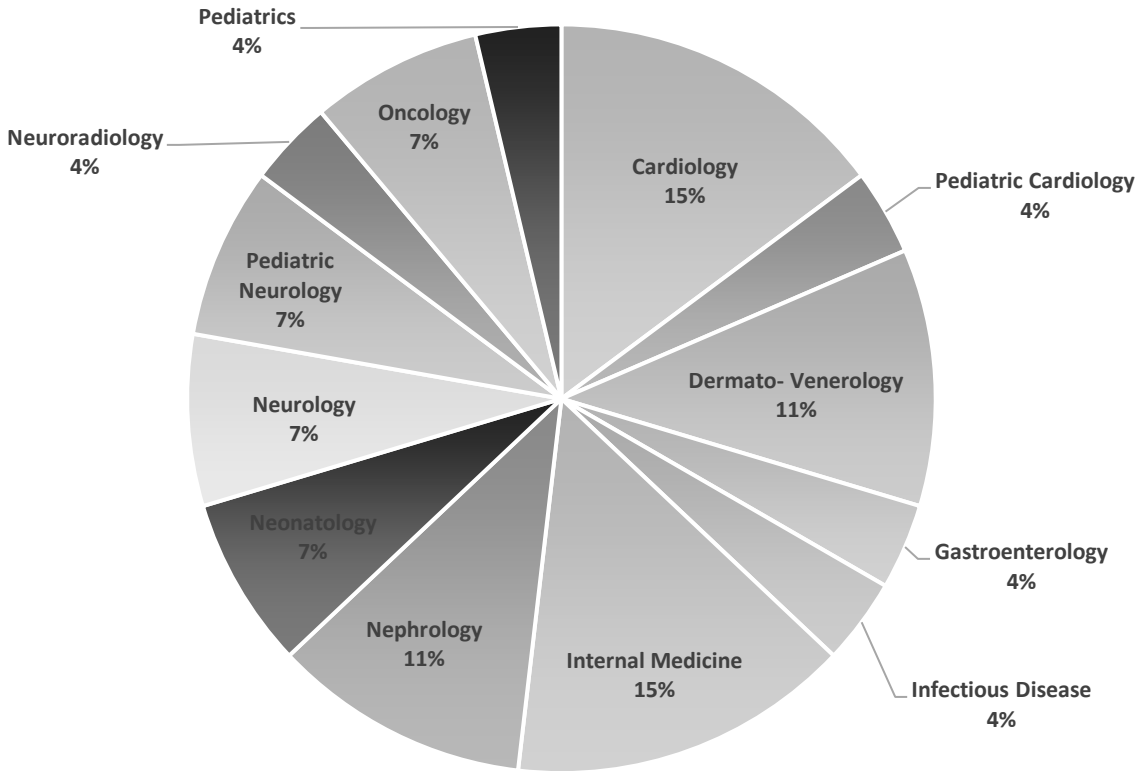


**Figure 2.** Distribution of approved clinical trials/studies per therapeutic area/medical specialty in 2019[3]

#### 1.2.1.2. Epidemiology and Statistical Analysis Office

The Epidemiology and Statistical Analysis Office (ESAO) gives support to the investigator-initiated studies. It supports CHULC's investigators through every step of the process from the study design to the publication of results, providing services that include offering an outlook on the feasibility and scientific adequacy of the study, support in study design and data management, epidemiological and statistical analysis, support in result interpretation and lastly the publication and release of the results. Presently, the ESAO is coordinated by Ana Luísa Papoila, PhD and Daniel Virella, MD.

Since the creation of the ESAO, in 2010, the Research Unit supported 519 projects, including academic thesis from CHULC´s investigators (Table 2). As a result from this support, 94 peer-review articles, almost all indexed in PubMed, were published since 2010, in which members of this office have been acknowledged as co-authors[6].

**Table 2.** Research Unit's support to new projects in 2019 and the total from 2010 to 2019 (10 years) [6]

| Year | Master Thesis | Doctoral Thesis | Others | Total |
|---|---|---|---|---|
| **2019** | 1 | 4 | 35 | **40** |
| **2010-2019** | 38 | 67 | 414 | **519** |

#### 1.2.1.1. Office for Registry and Support of Projects

The Office for Registry and Support of Projects (ORSP) centralizes the registration of CHULC's investigation, responding to the national official survey "Inquérito ao Potencial Científico e Tecnológico Nacional" (IPCTN), which is annually requested by the Direção-Geral de Estatísticas da Educação e Ciência (DGEEC). This office is coordinated by Salomé de Almeida, PhD.

Besides this, the ORSP also gives assistance to researchers in the search for grants, funding and application submission.

## Research Registry and Report

In 2019, the survey IPCTN18 addressed the clinical research performed during 2018, reporting a total of 528 projects, involving 803 investigators (Table 3). The typology of this projects is shown in Table 4[7].

**Table 3.** Registry of scientific activity and investigation in CHULC in the year 2018 in all 6 hospitals[7]

| Active R&D Units | R&D Units with project registry | Number of investigators | Number of projects | Number of articles | Congress Participation |
|---|---|---|---|---|---|
| 44 | 44 | 893 | 528 | 319 | 1018 |

**Table 4.** Typology of investigation projects active in 2018[7]

| Project Type | Total |
|---|---|
| **Interventional Studies** | **113** |
| Clinical Trials with Medical Devices | 3 |
| Phase II Clinical Trial | 4 |
| Phase III Clinical Trial | 66 |
| Phase IV Clinical Trial | 7 |
| Diagnostic Procedure | 3 |
| Therapeutic Procedure | 30 |
| **Observational Studies** | **415** |
| Retrospective descriptive analysis | 32 |
| Satisfaction Study | 6 |
| Epidemiological Study | 107 |
| Other Study Type | 116 |
| Diagnostic Procedure | 61 |
| Therapeutic Procedure | 93 |
| **Total** | **528** |

The IPCTN survey has recorded an annual increase in the number of projects from 2008 to 2018, placing CHULC in a high-ranking position, among other leading national health institutions (usually within the first four positions among approximately 120 public and private hospitals). This ranking is based in three

measures: volume of expenditure on R&D, volume of expenditure on R&D in clinical medicine and number of full-time researchers[7].

#### 1.2.1.2. Secretariat

The Secretariat provides special assistance to the CTU regarding the submission process of clinical studies. It also offers administrative support to the other offices in the Research Unit.

## 1.3. Clinical Research: an overview

This section presents a brief picture of the current Pharmaceutical R&D process, from the early stages of drug discovery to the pharmacovigilance procedures after approval. Furthermore, it describes the current clinical research process in Portugal and a review of the literature about clinical research in children.

Clinical research includes patient-oriented research, epidemiological and behavioural studies, outcomes research and health services research. Patient-oriented research is research conducted with human subjects where an investigator directly interacts with the subject[8]. Clinical trials involving drugs are included in this definition and were the main focus of the internship.

### 1.3.1. Drug Development: from lab to shelf

The R&D process for a new drug is lengthy, extremely regulated, expensive and always comes with an associated risk of failure. Generally, a new medicine may take 10 to 15 years to successfully come to market[9,10,11], with an estimated median cost of 1.2 billion euros to 3.2 billion euros in R&D, these values also include expenditures on failed trials[12,13].

A drug development plan should include all stages of the development of a pharmaceutical product from target selection across to post-approval activities. Although there is not a standardized method for developing a new drug, the whole process tends to follow a common pattern which can be divided into a number of

different stages that normally involve drug discovery, preclinical development, clinical development and approval processes schematically represented in Figure 3 and further described below[14,15,16].

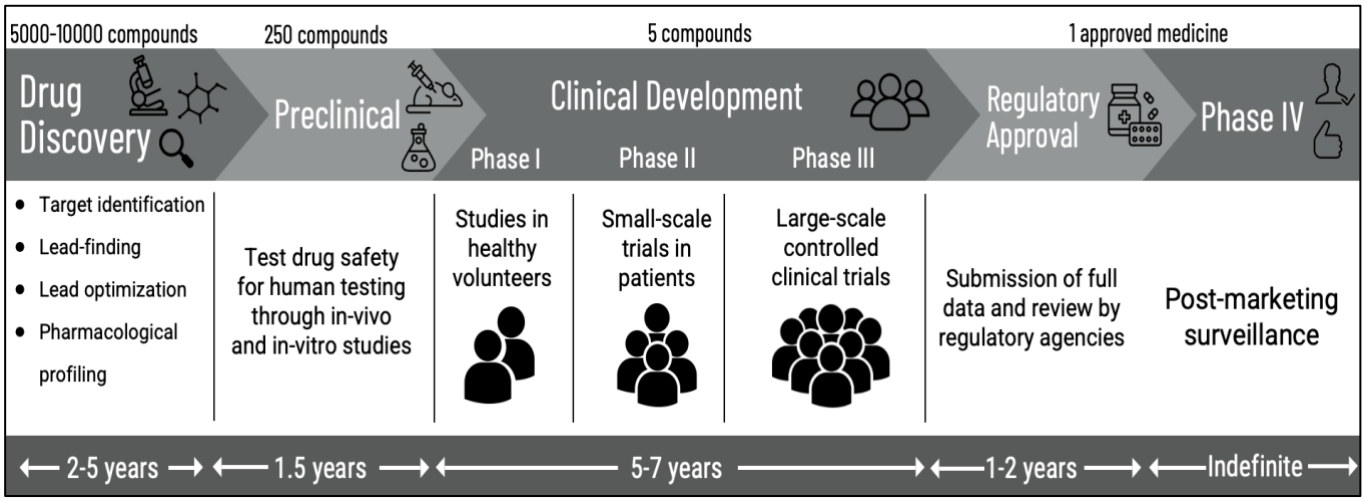


**Figure 3.** Drug development process adapted from [9][15][16]

The majority of pharmaceutical companies start by identifying an unresolved medical need or potential marketing opportunity and define the most adequate strategy to address that need/opportunity[9,17,18].

## Drug Discovery

Drug discovery is a multidisciplinary stage of the drug development process that requires cooperation among several scientific disciplines. The early stages of drug discovery start with an understanding of how the body works at a cellular and molecular level, as well as the disease/condition in study, as thoroughly as possible and use those findings to help in determining how a drug might be used for preventing, treating or curing a disease/medical condition. These conclusions will provide the researchers with a target to advance to the next steps in drug discovery that may include lead-finding, lead optimization and pharmacological profiling. [10,17]

At this level, the number of potential candidates molecules is significantly reduced and only about 250 compounds advance to next stage, preclinical development, for further testing[16,19].

## Preclinical Studies

The aim of preclinical development is to make sure that the candidate compounds meet every safety requirement, in order not to cause any serious harm in humans[15,20,21]. To assess these requirements scientists carry out two types of studies:

- ***in vitro*** tests, experiments conducted in a laboratory;
- ***in vivo*** tests, studies conducted in living cells, tissue cultures and animal models.

At the end of this phase, researchers should have a better understanding of how the drug works and the potential side effects on the human body. Based on this knowledge, only around 5 compounds are deemed safe by researchers and ready to advance for human trials[17,19].

Before entering the clinical development stage, the pharmaceutical company must file a Clinical Trial Application[22], in European countries, or an Investigational New Drug Application[23], in the United States of America, to the competent authorities, containing all the required information and documentation[18,24].

## Clinical Development

Clinical development is the point at which all the previously collected data from drug discovery and preclinical studies are put into medical practice to understand whether or not the scientific theory can be translated into a safe and effective new medicine for patients[19]. In order to obtain marketing approval from the national regulatory agencies, a new drug for human use must first undergo a series of clinical trials[11].

A clinical trial is defined as a research study in which human subjects are assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes, essentially it is an investigation of human subjects under experimental conditions[25,26]. Pharmaceutical clinical trials are categorized into four phases: Phase I, Phase II, Phase III and Phase IV. Each phase involves specific requirements that address target

population, inclusion/exclusion criteria, design features and outcomes, which must be well planned for the trials to be successful[10,11,26]. These four phases are summarized in Table 5.

**Table 5.** Clinical trial phases (based on ICH E8: general considerations for clinical trials) [10,11,27]

| | |
|---|---|
| **Phase I** | **Type of Study:** Human Pharmacology |
| | **Objective:** test safety and toxicity of the pharmaceutical drug |
| | **Target population:** Healthy volunteers (20-80) |
| | **Average Duration:** 1.5 years |
| **Phase II** | **Type of Study:** Therapeutic Explanatory |
| | **Objective:** determine effectiveness in condition or disease of interest; define appropriate dose |
| | **Target population:** Patients (several hundreds) |
| | **Average Duration:** 2 years |
| **Phase III** | **Type of Study:** Therapeutic Confirmatory |
| | **Objective:** Demonstrate/confirm efficacy; establish safety profile |
| | **Target population:** Patients (from several hundreds to several thousands) |
| | **Average Duration:** 2.5 - 5 years |
| **Phase IV** | **Type of Study:** Therapeutic use (post-approval) |
| | **Objective:** refine understanding of benefit–risk relationship in general or special populations and/or environments. |
| | **Target population:** Patients (variable) |
| | **Average Duration:** Variable |

Clinical trials must be highly controlled in terms of the safety and privacy of trial subjects. Every member of the research team that will interact directly with the subjects must be certified in **Good Clinical Practice**[28], following the guidelines

established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Before starting any trial procedures, the research subject (or his/her legal representative, when applicable) must be informed, by the investigator, about every important aspect of the trial and voluntarily decide to accept or decline participating in the trial. After analysing all the information provided, if the patient decides to enter the trial, the investigator must present an informed consent form (ICF) for him/her to read, date and sign[28].

## Marketing Authorization Application

On the latest version (July 2019) of the European Commission Notice to Applicants, Volume 2A - Procedures for Marketing Authorization it is stated that: "A marketing authorization lays down the terms under which the marketing of a medicinal product is authorized in the EU. A marketing authorization is composed of:

- a decision granting the marketing authorization issued by the relevant authority;
- a technical dossier with the data submitted by the applicant in accordance with Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007." [29]

The Marketing Authorization Application (MAA) compiles evidence that will be submitted as a dossier and applicants are required to use the Common Technical Document (CTD) format. The CTD encompasses all the necessary data on efficacy, safety and quality of the pharmaceutical product the MAA is intended for and it is organized into five different modules[24,30]:

- **Module 1** (Administrative and Prescribing Information): this module should contain documents that are specific to each region, such as, application forms or the proposed label for use in the region.

- **Module 2** (Summaries): this module contains a general introduction to the pharmaceutical product, including its pharmacological class, mode of action and intended clinical use. An overall summary of quality and an overview of the nonclinical and clinical summaries must also be included here.
- **Module 3** (Quality): this section includes the documentation and general information concerning the pharmaceutical substance, its manufacturing process, specifications, quality control, stability, among others. This information should be presented un the structured format described in Guideline M4Q[31].
- **Module 4** (Non-clinical Study Reports): this segment covers reports on animals and *in vitro* tests which must be presented in the order described in Guideline M4S[32].
- **Module 5** (Clinical Study Reports): every human study reports and related information should be included this module and be presented in the order described in Guideline M4E[33].

A diagrammatic representation of the organization of the CTD is presented below:

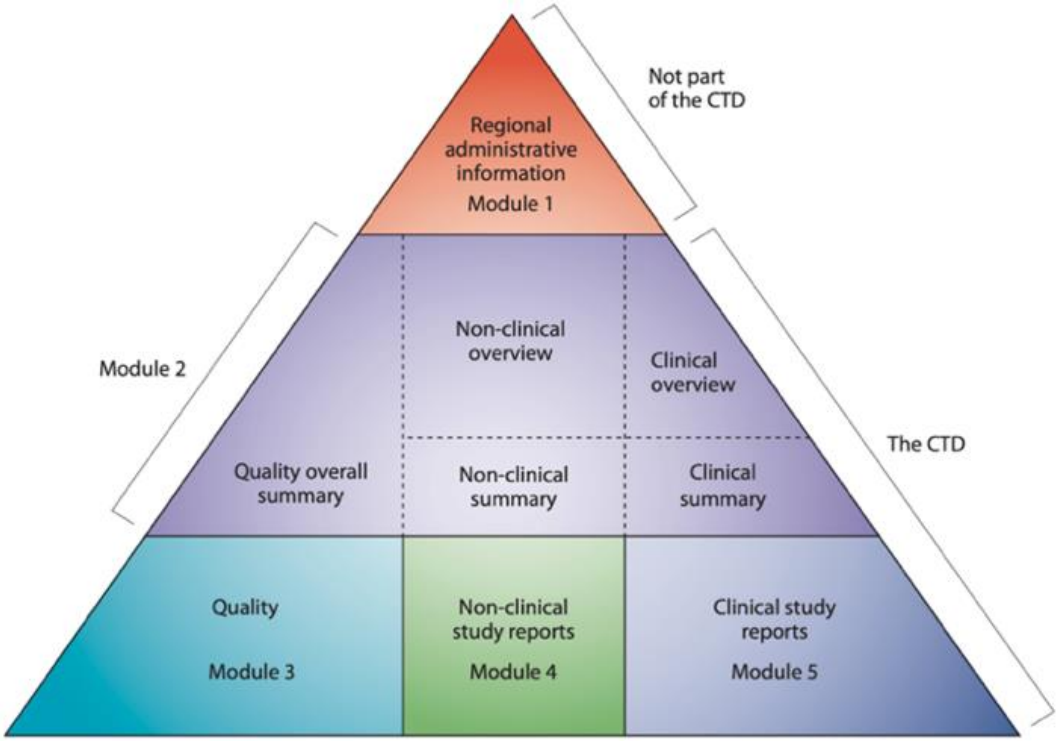


**Figure 4.** The CTD triangle

Post-Approval Research and Monitoring

After a new medicine is available in the market, post approval studies are necessary to monitor safety and possible long-term side effects. Thus, phase IV, also known as post-authorization study (PAS), or therapeutic use studies, are required by regulatory authorities[27].

### 1.3.2. Other clinical studies types

Besides clinical trials, there are several other different types of clinical studies. Broadly, clinical studies can be divided into two categories: studies without intervention (observational studies) and studies with intervention (experimental studies, such as clinical trials) [34].

Observational studies

In clinical studies without intervention, the prescribed medication or medical device used needs to be completely dissociated from the participation in the study[35]. Unlike clinical trials, that are always prospective, observational can be both prospective or retrospective. There are three types of observational studies:

- cohort studies
- case-control studies
- cross-sectional studies

Case-control and cohort studies measure disease occurrence and the possible association with an exposure over a certain period of time. In cross-sectional studies this relationship between the exposure and disease occurrence cannot be established, as the examined data is only at one particular timepoint[36].

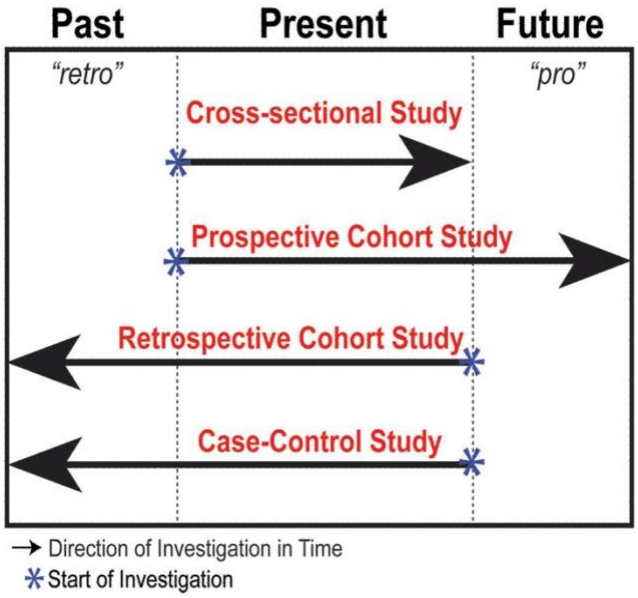


**Figure 5.** Temporal Design of Observational Studies

### 1.3.3. Clinical Research in Portugal

Regulatory framework and approval process

In Portugal, clinical research is currently ruled by the legal regime established by the Law no 21/2014, of April 16th, altered by the Law no 73/2015, of July 27th. This law has revoked the Law no 46/2004, of August 19th, transposing into the national law the Directive no 2001/20/EC of April 4th, 2001 of the European Parliament and of the Council[37].

According to European guidelines, and under the Portuguese legislation, aforementioned, the ethical and regulatory authorities are responsible for the evaluation and approval of clinical studies. In Portugal, the conduction of clinical trials is subject to the National Authority of Medicines and Health Products, I.P. (INFARMED) authorization and to the approval of the National Ethics Committee for Clinical Research (Comissão de Ética para Investigação Clínica - CEIC). Specifically, the INFARMED is the competent authority for the approval of clinical trials, clinical studies with medical devices, cosmetics and body hygiene[35,37]. As for the ethical evaluation, the CEIC is in charge of assessing clinical trials and clinical studies with medical devices. Other studies must be submitted to the local ethics committee of the institution, for approval[35,38].

Data protection is assured by the application of European Regulation 2016/679 of the European Parliament and of the Council, of 27 April 2016, repealed Law No. 67/98, of 26 October, which was transposed into the Portuguese legal order Directive 95/46/EC. This regulation is known as the General Data Protection Regulation (GDPR) and has been applicable since May 25, 2018. The new personal data protection law is Law No. 58/2019 of 08 August and ensures enforcement of the GDPR[38].

Current Scenario

The study “Ensaios Clínicos em Portugal”, conducted by “Associação Portuguesa da Indústria Farmacêutica” (APIFARMA) concluded that, when compared to other countries with similar dimension, Portugal still has growth

potential, appearing behind in the number of clinical trials submitted per million inhabitants. The pharmaceutical industry is increasingly selective regarding the locations to conduct their clinical trials, giving priority to countries offering better conditions. Portugal is not among these countries and has been losing its competitiveness progressively[39].

In 2019, INFARMED approved 142 clinical trials with an average time for authorization of 34 calendar days, a reduction of 15% compared to 2018 (Figure 6). An increase in the number of Phase I and Phase IV clinical trials submitted in 2019 was also observed compared to 2018 (Figure 7). By the end of the 3rd quarter of 2020, 140 clinical trials had been already submitted, 121 of which were approved[40].

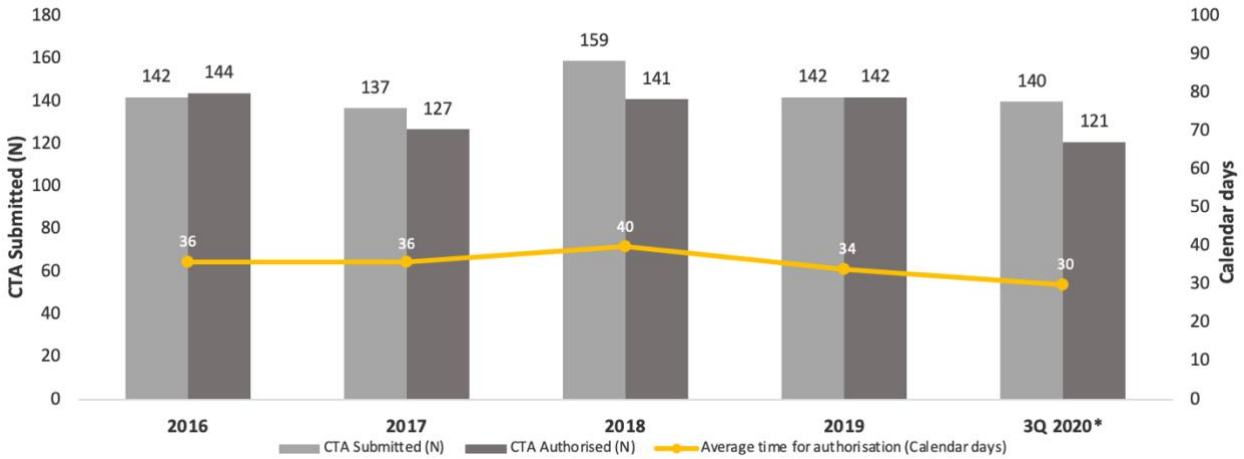


**Figure 6.** Clinical Trial Application (CTA) from 2016 to 2020 *Only refers to the 3rd quarter of 2020. Source: INFARMED

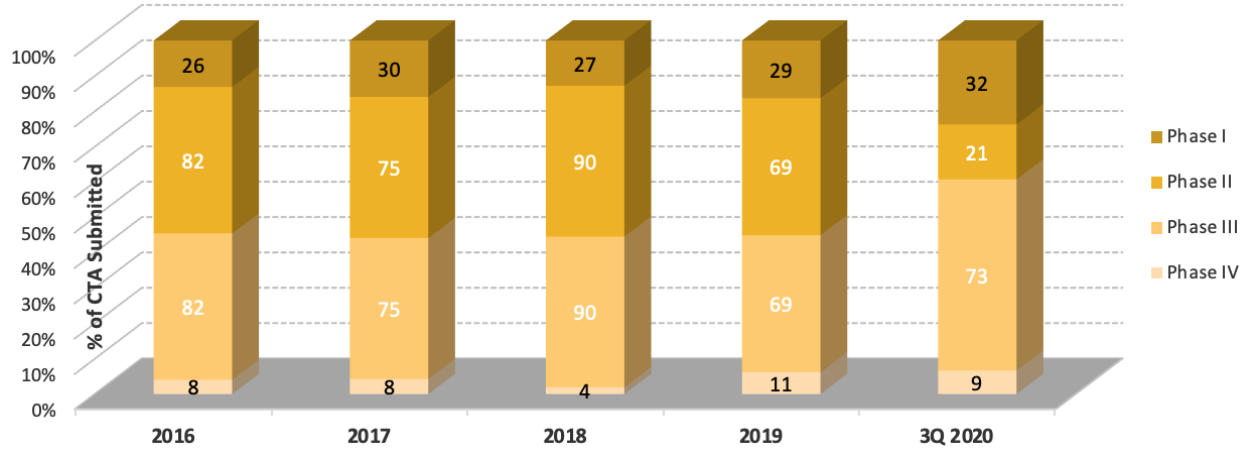


**Figure 7.** CTA divided by trial phases Source: INFARMED

## 1.4. Clinical Research in Children

**Introductory note:** the valuable experiences obtained during the training in the pediatric HDE and also in the pediatric cardiology service of HSM, were the main motivation to explore some aspects regarding paediatric clinical studies. A brief review of the literature was performed on this topic, from ethical issues to the perspective of children as participants.

### General aspects of clinical research in children

Over the years, advances in biomedical research have contributed to save the lives of children and to prolong their survival with quality of life[41]. However, the number of medicines labelled specifically for pediatric use is still very limited, which reflects the lack of investment in pediatric clinical research[42].

The pediatric population is considered vulnerable in the majority of regulatory documents on clinical research involving minors[43,44]. As a result, children have been excluded from research for many years and investigators are afraid of the potential harm this exclusion can bring. In consequence of few clinical trials, many drugs have not been sufficiently tested in this age group[42,45].

In recent decades, the number of clinical trials in adults and children has increased, contributing to the improvement in overall patient care. Despite this increase, the volume of clinical trials conducted in adults is much bigger than the ones conducted in children, resulting in insufficient data[46].This forces doctors to rely on the evidence obtained from adult clinical trials when treating a child, resorting to the “off-label” use of therapeutic drugs. Consequently, extrapolating adult drug doses to children increases the risk for adverse effects due to the fact the children’s physiology differs from adults in a multitude of ways[41,47]. Off-label treatment in pediatrics is frequent and widespread, with the most common reason for prescription being the use of an unapproved dose[48].A study focusing on off-label drug use in a Portuguese Pediatric Emergency Unit showed that in 28.1% of the study population, off-label drugs were used and among the children who received drug prescriptions, 46.1% were given at least one off-label drug[48]. Similar results

have been documented in numerous other studies throughout the scientific literature[46].

Therefore, the involvement of children and adolescents in clinical research is urgent and indispensable to study possible interventions for childhood specific conditions as well as, for clinical trials in drugs already tested in adults that might also be used for children or adolescents.

According to the International Ethical Guidelines for Biomedical Research[47], before undertaking research involving children, the investigator must ensure that:

- it might not equally well be carried out with adults;
- the purpose is to obtain knowledge relevant to the health needs;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child's capabilities;
- a child's refusal to participate or continue will be respected.

## Ethical and legal framework

Over the years, there is a growing commitment to pediatric studies and an evolution in pediatric legislation[49,50].The major ethical and legal instruments that guide clinical research in children are:

- Belmont Report;
- Declaration of Helsinki;
- ICH Topic E 11: Clinical Investigation of Medicinal Products in the Pediatric Population of 2001
- European Pediatric Regulation on medicinal products of 2006;
- Ethical considerations for clinical trials on medicinal products conducted with minors of 2008 (reviewed in 2017);
- Declaration of Ottawa on Child Health of 2009;
- ICH E11 (R1) Guideline on clinical investigation of medicinal products in the pediatric population of 2017.

- International Ethical Guidelines for Health-related Research Involving Human, Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (Geneva 2016).

## Classification of the pediatric population

The term “pediatric population” refers to children aged between birth and less than 18 years. Research involving this population includes a wide range of individuals with very different physical, cognitive and emotional capacities. Thus, it is necessary to separate the pediatric population into categories, normally age categories. The classification used needs to be flexible, in order to accommodate every child in a category and reflect the current knowledge of pediatric pharmacology. The ICH Topic E 11: Clinical Investigation of Medicinal Products in the Pediatric Population establishes one possible categorization[42]:

- preterm newborn infants;
- term newborn infants (0 to 27 days);
- infants and toddlers (28 days to 23 months);
- children (2 to 11 years)
- adolescents (12 to 16-18 years (dependent on region)).

In 2016, the CIOMS in collaboration with the WHO rearranged these categories, redefining the age group of children (2 to 11 years) and the age group of adolescents (12-18 years) into preschoolers (2-5 years), schoolers (6-9 years) and adolescents (10-18 years)[47].

## Consent and assent

The inclusion of humans in clinical trials requires their clear and conscious authorization, reflected on a signed written document, more commonly known as informed consent form (ICF)[35,51]. Unlike adults, children do not possess the necessary faculties to express their needs or defend their interests, to sign an ICF[46,52].

The process of obtaining the child's approval to participate in a clinical trial is the most important step, when possible. Informed consent for participation in pediatric trials is more complex than adult trials due to the fact that the informed consent is granted by proxy, from a parent or legal representative responsible for protecting the welfare of the child, under the Declaration of Helsinki. In addition to parental/legal representative permission, informed assent to participate in research must also to be obtained from the child, when he/she presents the cognitive abilities to make a conscious decision regarding their well-being[47,50].

As mentioned above, a pediatric subject is legally unable to provide a valid informed consent and is dependent on his/her parent(s)/legal representative to assume responsibility for their participation in any clinical studies. Nevertheless, whenever the child is considered able to assent, it should be obtained, preferably in writing for literate children. Evaluating the capacity and autonomy of the child to give their assent is the investigator's responsibility[51]. When making this decision, there are several factors that must be taken into consideration besides the child's age. Such factors include the personal circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation[47]. The lack or absence of expression of agreement or disagreement must not be interpreted as assent[42]. If the participant becomes legally capable to consent during the course of the study, his/her decision to continue or discontinue participation in the clinical study overrules the decision of their parents or legal representatives[47].

In Portugal, CEIC has recommended a model for obtaining informed consent in pediatric clinical trial, according to the age groups (Table 6)[51].

**Table 6.** Type of informed consent by age group, adapted from [51].

| Age | Type of informed consent |
|---|---|
| **<5 years** | Only the ICF from both parents or legal representative |
| **≥ 5 years and < 16 years** | Written assent form the subject* + ICF from both parents or legal representative |
| **≥ 16 years** | ICF from the subject + ICF from both parents or legal representative |

* if in the age group 12-15 years of age and considered ethically mature to assent by the investigator

When obtaining the informed consent/assent for pediatric research, the investigator must always explain the possible risk the clinical study might bring to the child. This risk needs to be presented and explained to the parents, but also the child of assent age. For better understanding, age-appropriate terminology should be used.

## Trial design

For a clinical study to be beneficial to those participating, and to the rest of the pediatric population in the future, it must be properly designed to ensure the quality of the data obtained. Children or adolescents participating in clinical studies are normally expected to benefit from them and that any possible risks are minimized[42,46,52].

The ICH E11(R1) guideline lists the most important factors to consider before starting a pediatric development program for a medicinal product. These include:

- the prevalence of the condition to be treated in the pediatric population;
- the seriousness of the condition to be treated;
- the availability and suitability of alternative treatments for the condition in the pediatric population;
- whether the medicinal product is novel or one of a class of compounds with known properties;
- whether there are unique pediatric indications for the medicinal product
- the need for the development of pediatric-specific endpoints;
- the age ranges of pediatric patients likely to be treated with the medicinal product;
- unique pediatric safety concerns with the medicinal product;
- potential need for pediatric formulation development;

As mentioned before in this report, clinical trials are composed of four consecutive phases. In contrast to clinical trial in adults, pediatric clinical trials tend to be deferred until the trials reach phase II or even III, as phase I trials are normally discouraged in children due to the unknown effects of the intervention being tested for the first time in humans[49]. While the deferral intends to protect children from

exposure to unnecessary harm, it also means a delay to the access of children to potentially useful medications. Phase IV post-marketing trials are rarely conducted in children[46,49].

The gold standard design for clinical trials is randomized, double-blind, controlled studies that helps minimize variability and bias and ensures valid quality results. Nevertheless, there are limitations to this standard as randomization might not be adjustable to all differences between individuals[46].

Additionally, the implementation of placebo control groups in pediatric clinical trial carries moral and ethical however, according to the American Academic of Pediatrics 2010 report “Guidelines for the Ethical Conducts of Studies to Evaluate Drugs in Pediatric Populations”, placebos can be considered ethical under the following five conditions[53]:

- there is no previous accepted therapy for the condition
- the commonly used therapy is of questionable efficacy
- the commonly used therapy is highly likely to produce adverse outcomes
- the placebo is used to find incidence of adverse effects by adding a new drug to the current treatment
- the condition has frequent exacerbations and remissions and current therapy is not effective.

## Recruitment challenges

The recruitment process in adult clinical trials is less difficult than in children, so most pediatric trials have small sample sizes with only 38% of 736 pediatric trials published from 1996 to 2002 having a sample greater than 100[49]. Nowadays, these trials have became more frequent, however sample sizes are still very small[46].

The most common barriers to child recruitment are parental consent and child assent, the study design/methodology, investigator’s reluctance to enrol children and funding issues[46].

## Children’s perspective of clinical research

The literature or evidence regarding the experience of children participating in clinical trials is very limited[54]. However, their view can contribute to a better understanding of what can be improved on in the development of medicines from their perspective.

A question-based survey conducted among children living in European Union countries between January and August 2015, shows that the majority of the study population would potentially agree to participate in a clinical trial because the investigational medicine might improve their own health or that of other children. The main reason present to refuse participating is the concern that the investigational medicine might be harmful to them[55].

A systematic review performed in 2015, showed that the most frequently mentioned motivating factors for children to participate in clinical research are personal health benefit, altruism and increasing comfort[56].

# 2. On-the-job Training

## 2.1. Experience as Clinical Research Coordinator

A CRC plays a core role on the ongoing management of clinical research, from start-up to close-out, collaborating with investigators to ensure studies are carried out in accordance with both the protocol and the principles of Good Clinical Practice(GCP)[57,58,59].

During the internship, the training as a CRC occurred in three different hospitals, within CHULC, in collaboration with health professionals from several different medical departments. The work was performed under the supervision of two very experienced CRCs: Ana Cunha, PhD with ongoing studies in both HSAC and HDE and Nurse Mafalda Selas with several ongoing studies in Cardiology (HSM).

Presently, in CHULC, there are several ongoing clinical trials and observational studies in almost every medical department across the six hospitals, as mentioned earlier in 1.2.1.1.. The main medical departments where the internship was conducted were: cardiology, internal medicine, neurology, oncology, ophthalmology, paediatric neurology. Over the course of the internship, fourteen clinical trials, one medical device trial and one observational study were followed, distributed as listed below:

- **Cardiology**: six clinical trials and one medical device trial;
- **Internal Medicine**: one observational study;
- **Neurology**: one clinical trial;
- **Oncology**: three clinical trials;
- **Ophthalmology**: two clinical trials;
- **Pediatric Neurology**: two clinical trials.

A more detailed description of the studies will be provided in sub-section 2.1.3..

### 2.1.1. Clinical Research Team

In the role of a CRC, there was the opportunity to interact with research teams from different departments, while acting as an intermediary between the intervening parties in a clinical study (figure 6).


**Figure 8.** The central role of a CRC

A research team is a group of people that, under the supervision of the Principal Investigator (PI) who is responsible for the team's activities, are in charge of the implementation and conduction of a clinical study. The team consist of investigators and all other professionals with direct and immediate participation in the studies[35].The members of a research team in the research centre are appointed by the PI, each having one or more assigned tasks, formally registered in the trial's delegation of authority.

Every element of a research team must be certified and comply with GCP principles. According to ICH Topic E6 Guideline for Good Clinical Practice, GCP principles are "a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected" [28].

### 2.1.2. Activities performed

Throughout this sub-section, a description of all tasks performed as a CRC, which are identical for all studies, is provided and a more detailed description of the

activities performed in each particular study (when applicable) is presented. The main responsibilities were the following:

- Assist in the assessment of clinical study feasibility;
- Participate in site qualification visits;
- Assist budget negotiation and internal submission process;
- Attend Investigator Meetings;
- Participate in site initiation visits;
- Organize and coordinate the execution of a clinical study;
- Collect register data in patient's Case Report Forms;
- Maintain stocks of study material and laboratory supplies;
- Manage biological samples;
- Fill out documents related to subjects' reimbursements;
- Prepare monitoring visits;
- Coordinate study close out visits;
- Report and notify Adverse Events (AE) and Serious Adverse Events (SAE)
- Archive study documents and maintain study documents updated and organised;

All these activities are described below, mentioning the tasks performed during the curricular training.

## Assist in the assessment of clinical study feasibility

The selection of clinical sites and investigators is a crucial aspect in the overall success of a clinical study. For this reason, many factors must be weighed in when making this decision.

When recruiting a site to conduct their clinical studies, the sponsor/CRO usually contacts either the CTU or the potential PI directly, with a feasibility questionnaire generally accompanied by a brief protocol overview. This questionnaire consists of several questions concerning the site's conditions (facilities, human resources, logistical conditions, previous experience in clinical research), the curriculum of the PI, the number of patients with the condition and the estimated number of recruited patients for the study. As soon as the questionnaire is received it should be

completed by the PI, with possible support from the CRC, and sent back to the sponsor/CRO for further evaluation.

During the internship, there was the opportunity to assist in the completion of one feasibility assessment questionnaire for an ophthalmology clinical trial.

### Participate in Site Qualification Visits

If a site passes the feasibility phase, the next stage is the conduction of a site qualification visit (SQV). This visit is done on-site by a clinical research associate (CRA), representing the sponsor/CRO, to assess if all the requirements are strictly met for the successful conduction of the study.

One SQV was attended, along with the CRC and the potential PI. The visit was performed by the CRA allocated to the clinical trial and, after the PI signed a confidentiality agreement, the monitor proceeded to present the trial protocol.

After this phase, the sponsor/CRO contacts the site to inform whether or not it was selected to conduct their clinical trial, usually via email.

### Assist budget negotiation and internal submission process

In CHULC, the responsibility of budget negotiation and consequent submission process is the responsibility of the Research Unit, more specifically the CTU. This means that every time the CHULC is chosen to host a new clinical study, before the recruitment phase can begin, a clinical trial agreement (CTA) must be signed by the intervening parties and this process is handled directly by the CTU of the Research Unit.

Currently, every clinical trial conducted in CHULC must have a signed and approved CTA (sponsor's template) and a signed and approved Financial Agreement (CHULC's template - current version 4, June 2019), before the study can start. The Financial Agreement is an internal document signed between the CHULC, the Sponsor and the PI which includes clauses regarding study duration, number of participants, estimated study charge, administrative costs and overall costs associated with the study. During my internship I did not have the opportunity

to assist in any budget negotiation with a sponsor, but the entire process was explained to me by the person responsible, Margarida Ferreira, PharmD.

Besides the CTA and Financial Agreement, according to CHULC's internal Standard Operating Procedures (SOPs), the submission file for sponsored clinical studies must also include:

- Letter addressed to the President of the Board of Directors requesting authorization for conducting the clinical trial at CHULC with complete information of the sponsor, PI, clinical site and the study's objective;
- Contact List (Sponsor and PI);
- Statement of the responsibility delegation from sponsor to the CRO representative (if applicable);
- Ethical statement by the competent ethics committee (CEIC for interventional studies and the Local Ethics Committee for observational studies);
- Authorization by INFARMED;
- Synopsis of the protocol in Portuguese;
- Protocol signed and dated by the PI;
- Case Report Forms;
- Investigator's brochure or summary of the medicine/medical device characteristics;
- Informed consent forms;
- Statements from the Clinical Director and the Medical Specialty Director relating to the adequacy of infrastructures, equipment and human resources;
- Statement of the pharmaceutical service;
- PI's *Curriculum Vitae* (CV);
- Insurance certificate.

While partaking in the submission process, some of the tasks performed included: the revision of the whole submission file; detection of missing documents or signatures; preparation of a digital copy of the relevant documents and sending them to the sponsor/CRO. During the curricular training period, there was the opportunity to assist in, seven submissions to the board of directors of the CHULC.

## Attend Investigator Meetings

Before the start of a study and after all the clinical sites have been selected, the sponsor/CRO holds an Investigator Meeting. This meeting, usually, occurs face-to-face in a pre-determined location allowing for the intervening parties of a clinical study to meet for the first time and learn from each other about how each site deals with recruitment, enrolment and retention of study subjects among other matters. The study protocol is reviewed in great detail, during the meeting, and all the attendees are allowed to ask questions[60].

During the training no Investigator Meetings occurred, however the whole process was explained, from personal experience, by the CRCs.

## Participate in Site Initiation Visits

A site initiation visit (SIV) is performed by the CRA at the clinical study site in the presence of the key study personnel. In this visit, the CRA should provide an overview of the key study aspects, focusing on its objectives, timeline, eligibility criteria, main procedures, study drug, eCRF, definition of AEs/SAEs and reporting procedures. In the presence of representatives from the laboratory and the pharmacy, the CRA must also explain its specific procedures (e.g., investigational medicinal product (IMP) accountability, temperature excursions, IMP prescription and dispensation, evaluation of compliance).

In the SIV, the CRA should also collect all the remaining necessary documents (e.g., CVs and GCP certificates from all team members) and guarantee that the trial staff delegation log, where all study staff members' significant study-related duties is recorded, and the training logs, where all trainings completed by study staff members are documented, are signed and dated by the end of the visit.

During the curricular training period, there was the opportunity to attend two initiation visits: an oncology clinical trial and an open-label clinical trial in neurology. On both occasions, due to scheduling incompatibilities, the visits were performed only in the presence of the CRA, CRC and both MEGIC students training at CHULC and later with the remaining members of the research team.

## Organize and coordinate the execution of a clinical study

After all the necessary documentation is collected and the CTA is signed and approved, as well as ethical approval granted, the sponsor informs the clinical site that is it authorized to enrol trial participants.

When the first patient is enrolled, the CRC is responsible for scheduling all the subsequent visits to the centre in the context of the clinical trial. Depending on the trial design, the number and type of visits may vary, however the most common visits are screening visit, baseline/randomization visit, intermediate scheduled visits, end of study visit and follow-up visit(s). These visits follow a tight window, in accordance with the trial protocol, that must be respected to ensure the best results. Each study visit has specific assessments that must performed, which are specified in the trial protocol' schedule of assessments. The CRC's assists the PI in ensuring that the study protocol is carefully followed and all the study procedures are completed accordingly.

Throughout the internship, scheduling and preparing subject visits to the centre was a common task performed for different clinical trials, distributed as described ahead, in section 2.1.3.. Everything was prepared ahead of time, such as the necessary forms to register clinical data, questionnaires or visit specific central lab collection kit. This involved contacts with the patients, investigators and all the hospital departments involved in each visit to ensure best possible synchronicity at the day of the visit.

## Collect and register data in patient's Case Report Form

According to ICH E6(R2) Guideline for Good Clinical Practice, a Case Report Form (CRF) is "a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject" [28].

Nowadays, CRFs are mostly electronic (eCRF) and the sponsor is responsible for designing the eCRF, in accordance with the number of visits or study procedures needed, and later providing its access to the investigators and coordinators.

Registering all the data collected in a study visit is a very important task performed by the CRC, and it must be done according to the source documents available. Source documents are original or certified copies of documents or records that contain all the accurate and verifiable data regarding the patient's visit (e.g., hospital records, laboratory results, subjects' diaries or evaluation checklists, pharmacy's dispensing logs).

In this internship, in CHULC, all the CRFs were electronic and relatively user friendly. After every patient visit, it was confirmed that all source documents were available before inserting the data in the eCRF. After registering the data in the eCRF, queries might appear. Queries are questions or discrepancies that need to be addressed as soon as possible. These queries might be generated immediately (e.g., a missing date) or generated by data monitors and CRAs that review the data in the eCRF in accordance with the trial protocol. The eCRFs of the several studies were accessed regularly to make sure all pending queries were promptly answered.

### Maintain stocks of study and laboratory supplies

Every clinical trial or observational study has specific study materials (e.g. study visit scripts, study drug dispensing forms, study questionnaires, SAE forms and other study specific documentation/forms) and laboratory supplies (e.g. sample collection kits, lab requisition forms, carton shipment boxes for sending samples at room temperature or in dry ice, specimen transport bags, waybills). It is, usually, part of the CRC's activities to guarantee that these materials are available and accessible throughout the entire study and whenever needed.

During the internship, this task was transversal to most studies and was performed regularly. Before every patient visit, an inventory of the missing or nearly expired laboratory kits was made in advance. If needed, the specific form for reordering provided by the sponsor/central lab with the necessary items would be filled out. This request for lab materials is currently mostly done using electronic platforms indicated by the sponsors.

Manage biological samples

Per protocol, blood and/or urine samples need to be collected in almost every study visit. These samples can be analysed by the hospital's local laboratory or by the central laboratory chosen by the sponsor (or both).

The first step for the samples to be sent to central laboratory analysis is, before collecting the sample, preparing the study kit. Each kit is visit specific and already comes with the collection tubes, urine cups (if applicable), transfer tubes, needles and the requestion form that must be shipped along with the samples. All tubes need to be labelled beforehand with the trial subject id and the requisition form needs to be filled out with the necessary information (e.g., subject id, year of birth, date of sample collection).

After the study kit is properly labelled, the samples can be collected. In both HDE and HSAC, the samples were collected and processed by a laboratory technician, however, in HSM these tasks were performed by the CRCs, as they were both nurses. The processing of the samples was done following the instructions in the laboratory manual provided by the sponsor's designated vendor.

The final step was the preparation of samples to send to the central laboratory, after all the samples were prepared and all the requisition form fields had been filled. The shipping process started with the preparation of the shipment box. The sample tubes were placed in the absorbent sleeves and then placed inside the specimen transport bag. If the samples were ambient, the shipment was at room temperature and it was only necessary to place the bag inside the shipment box, accompanied by the form. If the samples were frozen, the shipment required dry ice that needed to be ordered in advance. The procedure for frozen samples was the same, but an additional Styrofoam box was used inside a carton shipment box. For these shipments, the bag was placed inside the Styrofoam box and then covered with dry ice. After all the samples were prepared for shipment, it was necessary to request the pick-up from the carrier assigned by the sponsor. To schedule this pick-up, a call to customer service was performed, providing them with the sponsor's account number. At the scheduled time, a carrier collected the samples, taking the shipping documents provided by the sponsor that included an airway bill with all the correct

information regarding the shipper and the receiver. Lab results would later be available online in the central laboratory's platform.

This task was performed in four different trials, with different local and central laboratories. The main differences identified between the different central laboratories were in the identification of the tubes. One laboratory had the labels already on the tubes and only needed to write the subject id, while in the other's it was necessary to fill out the labels and then place them on the tubes vertically, without covering the cap.

### Fill out documents related to subjects' reimbursements

According to Law no 21/2014, subjects participating in a clinical trial cannot be granted any incentives or financial inducements. However, expense reimbursement and compensation of losses incurred from the participation in the study are allowed. As patients should not have any additional expenses resulting from taking part in a clinical trial, every expense related to transportation and food in visit days, is covered by the sponsor. Compensation for the hours/days missed from work to attend the study appointments should also be applicable.

During the internship, the reimbursements of patients in two clinical trials, were handled. Before starting, all the receipts that the patient presented were gathered and it was confirmed that the dates matched the dates the patient had a study visit. To maintain the patient's privacy, the reimbursements were done by the hospital and not directly by the sponsor. To facilitate this process, the CHULC developed an internal form with the identification of the study, the description of the expenses (date, category and value), the beneficiary of the reimbursement and his/her banking information. After the CRC filled out this form, it was sent to the finance department, checked for inconsistencies and, after being anonymized, was sent to the sponsor/CRO for approval. Once the expenses were approved and paid, the finance department proceeded to the reimbursement to the patient's account.

## Prepare monitoring visits

Monitoring visits are fundamental for the sponsor to guarantee that the trial is being conducted according to protocol and that GCPs are respected. The main purpose of these visits is to perform source data verification (SDV), ensuring that the data collected is reliable and that the data inserted in the eCRF is in conformity with source documents.

Before the visit, it was confirmed that all the available and required data was properly introduced in the CRF and that there were no open queries. It was also confirmed that all the source documents were archived in the subject's files and that the Investigator Site File (ISF) was organized and updated. The visits were based at the CRC's office, where the CRAs reviewed all documents and CRFs during the day. If necessary, it would also be scheduled for the PI/investigator to speak with the CRA. At the end of the visit, after performing the SDV, the CRA would ask the CRC to clarify any doubts that came up during the visit and ask to make the necessary amendments to the source documentation and the CRF. Five monitoring visits were prepared and attended during the internship:

- one for an ophthalmology clinical trial (#15)
- one for an oncology clinical trial (#11);
- one for a neuropediatric clinical trial (#13);
- two for two different cardiology clinical trials (#5 and #6).

## Coordinate study close out visits

Although the opportunity to be present in a close-out visit (COV) did not occur, an overview of the visit was explained by the CRC responsible for the internship.

In a COV, the CRA comes to the centre for a final review of the ISF, drug accountability reconciliation and to confirm all study records are collected and archived. The CRC needs to inform the CRA where the study records will be archived.

## Report and notify Adverse Events and Serious Adverse Events

According to guideline ICH Topic E 6, an AE is “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”. AE can be any symptoms, signs or an abnormal result of an intervention.

Prior to enrolment, during the screening visit, the PI and the CRC document and record the subject’s medical history. Over the course of the study, any updates need to be reported in the eCRF, as well as, the occurrence of any AEs. AEs are reported in a special way, according to the study protocol. Data that must be registered includes:

- start date of the AE;
- relation with the study medication (possible/unlikely);
- severity classification (severe, moderate, mild);
- any medication or treatment that was administered for the event;
- end date of AE (if not ongoing).

If an adverse event results in death, endangering of the subject’s life, hospitalisation, prolonged hospitalisation or significant impairment[35],then it must be considered a Serious Adverse Event (SAE) and must be reported to the sponsor within 24 hours.

During the internship, several AEs were reported in different trials (see table 13) however, no SAE occurred.

## Organize, maintain and archive study documents

Maintaining the study documentation organized and updated was a very important task that was performed every week. This included the archive of documents from a patient visit to the site, as well as study documentation in the ISF.

### 2.1.3. Clinical trials and observational studies followed

In this segment of the report, a brief description (acronym, condition, phase and trial design) of the sixteen clinical studies followed during the internship in CHULC is presented. All the information provided is publicly available at ClinicalTrials.gov and is organized in six tables (Table 7 to Table 12) per medical department. At the end of this section, table 13 presents an overview the tasks performed per clinical study.

Cardiology

This part of the internship occurred over two weeks spent in the HSM cardiology department, under the supervision of nurses Mafalda Selas and Filipa Fernandes. During this period, three patient visits (#3 and #6) and two monitoring visits (#5 and #6) occurred. At the time a new platform for clinical studies registration was being tested in CHULC and registering data for seven studies was also a part of the internship.

**Table 7.** Clinical studies followed in the cardiology department

| Cardiology | | | | |
|---|---|---|---|---|
| # | Acronym (EudraCT number) | Condition | Phase | Trial Design |
| 1 | **EMPERIAL reduced (2017-004073-14)** | Heart failure | III | Randomized Double-blinded |
| 2 | **EMPERIAL preserved (2017-004072-59)** | Heart failure | III | Randomized Double-blinded |
| 3 | **ENTRUST-AF (2016-002683-14)** | Atrial Fibrillation | III | Randomized Open-Label |
| 4 | **RESHAPE (NA)** | Mitral Valve Insufficiency | NA | Randomized Open-Label |
| 5 | **TOMORROW (2016-001062-28)** | Pulmonary Arterial Hypertension | III | Randomized Open-Label |
| 6 | **PANORAMA-HF (2015-004207-22)** | Pediatric Heart Failure | II & III | Randomized Double-blinded |
| 7 | **PANORAMA-HF OLE (2018-004154-25)** | Pediatric Heart Failure | III | Open-Label |

## Internal Medicine

This observational study, EmERGE, is part of a project funded by the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement no: 643736[61].

The main task performed during the internship regarding this observational study was data introduction in the eCRF. This data included, ICFs, patient questionnaires and data collected over the patients visits to the centre (demographic data, visit month 0 or baseline, visit month 6 and visit month 12). A few hundred eCRF entries were made during the internship.

**Table 8.** Clinical studies followed in the internal medicine department

| Internal Medicine | | | | |
|---|---|---|---|---|
| # | Acronym (EudraCT number) | Condition | Phase | Study Design |
| **8** | **EmERGE (NA)** | HIV | NA | Observational |

## Neurology

This clinical trial, Alithios, was conducted in the Neurology department of HSAC and was at the extension phase, which is when all the subjects enrolled in a clinical trial start taking the study drug even if they were not originally in the treatment arm. There was the opportunity to be present at the SIV, which allowed for a better understanding of the trial protocol and study procedures. During the internship, only one patient visit occurred which was introduced in the eCRF, with supervision of the responsible CRC.

**Table 9.** Clinical studies followed in the neurology department

| Neurology | | | | |
|---|---|---|---|---|
| # | Acronym (EudraCT number) | Condition | Phase | Trial Design |
| **9** | **Alithios (2017-004703-51)** | Relapsing Multiple Sclerosis | III | Open-Label |

## Oncology

There were two ongoing trials assigned to Ana Cunha in the oncology department of CHULC:

- Clinical trial **#10** was the one where most internship time was spent, as the visits were more frequent (5 visits), however in this trial the only tasks were assisting laboratory technicians in sample handling and shipment as there was another CRC in charge of scheduling visits and data entering was done by the investigators;
- Clinical trial **#11** had a monitoring visit where some pending issues and open queries were resolved.

Clinical trial **#12** had the SIV during the internship period, however it did not start until after the training period had ended.

**Table 10.** Clinical studies followed in the oncology department

| Oncology | | | | |
|---|---|---|---|---|
| **#** | **Acronym (EudraCT number)** | **Condition** | **Phase** | **Trial Design** |
| **10** | **7465-CL-0301 (2017-003344-21)** | Ureteral Cancer<br>Urothelial Cancer<br>Bladder Cancer | III | Randomized<br>Open-Label |
| **11** | **Javelin (2015-003262-86)** | Urothelial Cancer | III | Randomized<br>Open-Label |
| **12** | **THOR (2017-002932-18)** | Urothelial Cancer | III | Randomized<br>Open-Label |

## Neuropediatric

The Elektra clinical trial was the one with most dedicated internship hours and that offered the most complete coordinating experience, taking place in HDE. There was already one patient enrolled in the trial at the start of the internship (and one screening failure). However, there was the opportunity to follow the screening of a new patient and be present in the subsequent study visits (2 visits).

In the screening/baseline period of this trial, there was a patient diary that needed to be filled out by the child´s parents with the total number of seizures during a certain period of time. This data was analysed when the patient came to the centre for the randomization/dosing day, in real-time, by someone off centre assigned by the sponsor that gave the green light for the CRC to randomize the patient through an Interactive Web Response System (IWRS).

During the internship, a total of three patient intermediate scheduled visits to the centre occurred with similar schedules of assessments:

- Nursing consultation
- Clinical laboratory testing (with sample collection pre and post IMP administration)
- Clinical consultation with a study investigator
- Study drug dispensing

A few days after these at-site visits, a telephone contact was made to access if there were any adverse events or changes in the concomitant medication. All the data collected at these visits were introduced in the eCRF as soon as possible.

There was also one monitoring visit during the training period.

**Table 11.** Clinical studies followed in the neuropediatric department

| **Neuropediatric** | | | | |
|---|---|---|---|---|
| **#** | **Acronym (EudraCT number)** | **Condition** | **Phase** | **Trial Design** |
| **13** | **Elektra (2018-002484-25)** | Epilepsy (Dravet Syndrome/Lennox-Gastaut Syndrome) | II | Randomized Quadruple-blinded |
| **14** | **Endymion (2018-002485-39)** | Epilepsy (Dravet Syndrome/Lennox-Gastaut Syndrome) | II | Open-Label |

## Ophthalmology

At the beginning of the internship, the ROBIN clinical trial was already ongoing at the ophthalmology department of HSAC, but without any recruited patients. There was the possibility to participate in a patient screening visit, however, the patient failed the visual acuity exam and was considered a screening failure, not continuing in the trial. In this trial the inclusion/exclusion criteria were particular difficult to follow and all seven patients selected, prior to the beginning of this internship, were screening failures.

Later, the recruitment was closed by the sponsor and there was a monitoring visit to verify all the data collect to date. Since the trial would not be recruiting any more patients and did not include any, the CRA made an inventory of the study material still at site and that needed to be returned.

The Pulsar clinical trial had a qualification visit during the internship that is described in the previous section.

**Table 12.** Clinical studies followed in the ophthalmology department

| Ophthalmology | | | | |
|---|---|---|---|---|
| # | Acronym (EudraCT number) | Condition | Phase | Trial Design |
| **15** | **ROBIN (2016-002971-91)** | Diabetic Retinopathy | II | Randomized Double-blinded |
| **16** | **PULSAR (2019-003851-12)** | Neovascular Age-Related Macular Degeneration | III | Randomized Quadruple-blinded |

Overall distribution of tasks

In the table below, a distribution of the tasks, previously described, per clinical study is presented:

**Table 13.** Overall distribution of clinical studies followed per tasks performed

| Task | Clinical Studies | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Feasibility | | | | | | | | | | | | | | | | |
| Site Qualification Visits | | | | | | | | | | | | | | | | X |
| Budget negotiation and internal submission process | | | | | | | | | | | | | | | | |
| Investigator Meetings | | | | | | | | | | | | | | | | |
| Site Initiation Visit | | | | | | | | | X | | | X | | | | |
| Execution of a clinical study | | | | | X | | X | | X | X | | | X | X | X | |
| Register data in CRFs | | | | | X | | X | X | X | X | X | | X | | X | |
| Biological sample management | | | | | X | | X | | X | X | | | X | | X | |
| Maintain stocks of study material and laboratory supplies; | | | | | | | | | X | X | | | X | | X | |
| Subjects' reimbursements | | | | | | | | | | | | | X | | X | |
| Monitoring visits | | | X | | | | X | X | | X | X | | X | | X | |
| Close-out Visits | | | | | | | | | | | | | | | | |
| AEs and SAEs | | | | | | | X | | X | X | X | | X | | X | |
| Archive study documents | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

## 2.2. Other activities

Team meetings

During the internship, there were several team meetings to discuss the overall progress of the Research Unit, at least once a month.

Besides these meetings, there was also the opportunity to participate in a meeting with most of the CRCs working in CHULC. This meeting was very important as it gave a more tangible vision of the clinical research performed in CHULC as well as the issues and difficulties that CRCs faced if their practice.

Complementary learning

In the CRC meeting previously mentioned, it was possible to view a presentation on the topic “Risk based monitoring”, conducted by Ângela Papa, PharmD, from the CRO PPD.

On the 12th of December 2019, there was the opportunity to participate in a workshop on “Pharmacovigilance and spontaneous notification” (see annexe C), conducted by the Pharmacovigilance Unit of Setúbal and Santarém.

# 3. Discussion

Before being released to the market, every new medicine needs to go through a series of studies to obtain the necessary data and evidence regarding its safety and efficacy. As previously mentioned, these studies are clinical trials, which were the main focus of this internship, along with observational studies. Besides clinical trial coordination related tasks, there was also the opportunity to participate in early stage activities within the Research Unit of CHULC.

Unfortunately, due to the COVID-19 pandemic, the internship was shorter than initially anticipated. However, hence the internship occurred in a clinical research unit, it was possible to acquire a great amount of knowledge and differentiating skills over a short period of time.

As presented in the section 1.2.2, CHULC's Research Unit was created in 2009 and has since become an organized multidisciplinary team, with each member being assigned very specific functions and responsibilities. The integration process in a new environment with a new team and well-established working methods and circuits was the first challenge to overcome in this internship. Over time, with a better understanding of the working structure, each person's role and the procedures applied, it was easier to feel part of the team.

When the internship started, there were already dozens of ongoing studies across the CHULC and during the training new studies were submitted or approved almost every week. Sponsors identify one of CHULC's six hospitals as potential sites for theirs study because of the experience, qualified staff, suitable facilities, number of patients and adequate equipment and resources. While training at CHULC it was possible to witness the motivation and dedication to attract sponsors and new studies. One such example is the continuous time tracking in the submission and approval process in order to minimize time and be competitive.

The major role and main objective of this internship was being able to conduct a clinical trial as a CRC in the frenetic and unpredictable hospital scenario, this being one of the biggest difficulties faced. Each clinical study had a different team, with different methods and different organization. Unavoidably, there was the need adapt to each team, and even each study member for things to work. Time management and organization were two major skills that were highly improved throughout this

internship as every study visit had to be carefully prepared in advance so that no protocol required procedures were overlooked and that the patient had the least amount of inconvenience while at the centre.

Besides the clinical team at the study site, it was also necessary to communicate and work with the sponsor/CRO in order to achieve the best results. A healthy interaction between the CRA and the CRC greatly improves the efficiency the flow of the whole trial. It was a very enriching opportunity to be present in so many monitoring visits performed by different CRAs for different sponsors, as it was possible to understand better the work performed “on the other side”. Thus, another one of the initially established objectives was also achieved as small contact network was formed.

Possibly the most important contact, as a CRC within a clinical study, would have to be the relationship with the patients. This was probably the biggest challenge encountered during the training period as it was not always easy to disconnect from the emotional side when dealing with the more severe cases. This proved to be particularly true while working in the clinical trials that involved children and that was the main motivation to search more about the matter and make the bibliographic review of this report on the topic “Clinical Research in Children”. From this review, it was possible to conclude that a lot more can still be done to protect children through medication that is targeted to them instead of just protecting and preventing them from participating in clinical trials, that in the long run will do more harm than good.

Lastly, as previously mentioned and also identified as one of the internship objectives, personal/soft skills were greatly developed along the course of the training. Communication is very important in this area as it is crucial that the information does not “get lost in translation” and it should be adapted to the person with whom the conversation is held. Thus, good communication skills were deeply improved in these short months. Another extremely important skill to have while working as a CRC and in clinical research, in general, is teamwork. Working as a team in clinical trials is crucial for everything to run smoothly. This was a skill that was promoted every day and transversal to everything, not just clinical trial-related matters. Time management, autonomy and organizational skills had already been

mentioned along this discussion, but those were also skills enhanced during the internship.

The completion of this internship enabled a clearer and broader vision about the initiation, conduction and close-out of clinical trials in a public hospital setting. The clinical trials coordination was the primary focus of this internship, during which difficulties were experienced, challenges were found, and strategies were developed to battle adversities, and, in the end, it left a great sense of accomplishment and a lot of newly acquired experience that will be essential in the future.

# 4. Conclusion

Clinical research is a major contributor to the progress made in the health area and all elements of a research team are essential to study success and CRCs are a part of that.

After concluding most of the curricular component of MEGIC, it was vital to see and apply all the acquired knowledge in the field and the internship, as a CRC, performed in the Research Unit of CHULC proved to be a very complete experience.

Throughout the training, it was possible to follow all activities performed before, during and after the submission of a clinical study to regulatory authorities in a wide variety of studies. All the knowledge, skills and competences acquired during MEGIC were extremely helpful throughout this internship and were only enhanced by it as it was possible to learn how to proceed in real work circumstances. Additionally, it was possible to identify particular areas of interest and establish a working contact network. Therefore, it is viable to assume that all the previously set internship objectives (section 1.1.) were fully achieved and autonomy was achieved in the execution of most tasks.

Overall, this internship was an extremely enriching opportunity and although it was only a few months, it contributed immensely to personal and professional growth and set the tone in this journey in Clinical Research.

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# 6. Annexes

**Annexe A.** Declaration of internship duration and workload by the competent service of the Host Institution

DECLARAÇÃO

Para os devidos efeitos se declara que a aluna do Mestrado em Gestão da Investigação Clínica **Maria Carlos Murça Elias Moreira** realizou um estágio curricular no **Centro de Investigação** do Centro Hospitalar Universitário de Lisboa Central, EPE, que incluiu atividades no âmbito da Coordenação de Estudos Clínicos. O estágio decorreu entre 30 de Setembro de 2019 a 10 de Março de 2020, perfazendo um total de 298 horas.

Lisboa, 26 de Fevereiro de 2021.

Coordenador do Centro de Investigação

**Prof. Doutor Luís Pereira da Silva**
(Orientador)

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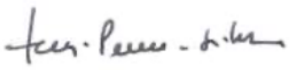
**Annexe B.** Supervisors declaration

PARECER

Na qualidade de orientador da aluna de mestrado **Maria Carlos Murça Elias Moreira**, no 2.º Ciclo de Estudos conducente ao grau de Mestre em Gestão de Investigação Clínica, programa de colaboração entre a Universidade NOVA de Lisboa (Nova Medical School | Faculdade de Ciências Médicas - NMS | FCM, a NOVA Information Management School, Escola Nacional de Saúde Pública) e a Universidade de Aveiro, declaro que o seu Relatório de Estágio intitulado *"Internship Report in a Clinical Research Unit"* se encontra finalizado, reunindo as condições para ser apreciado e defendido.

Lisboa, 26 de fevereiro de 2021.

O Orientador



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**Prof. Doutor Luís Pereira da Silva**

**PARECER**

No âmbito curso do 2.º Ciclo de Estudos conducente ao grau de Mestre em Gestão de Investigação Clínica, Mestrado que resulta da colaboração entre a Universidade NOVA de Lisboa (Nova Medical School | Faculdade de Ciências Médicas (NMS | FCM), NOVA Information Management School, Escola Nacional de Saúde Pública) e a Universidade de Aveiro, e na categoria de Orientadora, venho por este meio declarar que o Relatório de Estágio , intitulado "Internship Report on a Clinical Research Unit" e realizado pela aluna Maria Carlos Murça Elias Moreira, se encontra finalizado, reunindo as condições para ser apreciado e defendido.

A Orientadora

_____

Prof. Doutora Nélia Gouveia

Investigadora Auxiliar da NOVA Medical School|Faculdade de Ciências Médicas da UNL
Professora Auxiliar Convidada da Universidade de Aveiro

Lisboa, 26 de Fevereiro de 2021

**PARECER**

No âmbito curso do 2.º Ciclo de Estudos conducente ao grau de Mestre em Gestão de Investigação Clínica, Mestrado que resulta da colaboração entre a Universidade NOVA de Lisboa (Nova Medical School | Faculdade de Ciências Médicas (NMS | FCM), NOVA Information Management School, Escola Nacional de Saúde Pública) e a Universidade de Aveiro, e na categoria de Orientador, venho por este meio declarar que o Relatório de Estágio , intitulado "Internship Report in a Clinical Research Unit" e realizado pela aluna Maria Carlos Murça Elias Moreira, se encontra finalizado, reunindo as condições para ser apreciado e defendido.

O Orientador

Data

26 FEV 2021

**Annexe C.** Certificate of attendance in the “Pharmacovigilance and spontaneous notification” workshop

Infarmed 25+

REPÚBLICA PORTUGUESA
SAÚDE

SNS
SERVIÇO NACIONAL DE SAÚDE

## Certificado de Formação

Maria Moreira

[Nome do formando]

Participou na Sessão **“Farmacovigilância e Notificação Espontânea”**, no âmbito do Sistema Nacional de Farmacovigilância, que se realizou no dia 10/12/2019, no Hospital Curry Cabral (Local da formação), com a duração de 1 hora.

Unidade de Farmacovigilância Setúbal e Santarém

Unidade de Farmacovigilância Setúbal e Santarém

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