INTERNSHIP REPORT AT A CLINICAL RESEARCH UNIT – CRU²C

The specifics of clinical research with radiopharmaceuticals

Tânia Sofia Codinha Petisca

An Internship Report submitted in partial fulfillment of the requirements for the Degree of Master's in Clinical Research Management

Master in Association:
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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Resumo

Este relatório descreve as atividades realizadas durante o estágio curricular na CRU^{2}C, a unidade de investigação clínica do Instituto de Ciências Nucleares Aplicadas à Saúde, Universidade de Coimbra.

O estágio teve como principal objetivo aplicar os conhecimentos adquiridos durante a componente letiva do mestrado em Gestão da Investigação Clínica e centrou-se em atividades de *Clinical Trial Assistant* and *Start-Up Specialist* em ambiente académico.

O relatório incluiu uma revisão bibliográfica sobre a investigação clínica, o panorama da investigação clínica em Portugal juntamente com a sua regulamentação e descrição da importância das unidades de investigação clínica. Em seguida, são analisadas as especificidades da Investigação Clínica com Radiofármacos. Nesse sentido, são apresentados os desafios da investigação Clínica com radiofármacos e discutidas possíveis oportunidades de melhoria na área, com o objetivo de impulsionar o desenvolvimento de novos radiofármacos e, por conseguinte, a sua aplicação na prática clínica. Por fim, são descritas as atividades realizadas no âmbito do estágio curricular realizado na CRU2C.

Em suma, poderá concluir-se que o estágio curricular atua como uma ferramenta essencial para adquirir experiência prática em gestão da investigação clínica, contribuindo para o desenvolvimento de competências necessárias para o trabalho nesta área.

Palavras-chave: Investigação Clínica, Regulamentação, Unidades de Investigação Clínica, Radiofármacos.

Abstract

This report describes the activities performed during the curricular internship at CRU^{2}C, the clinical research unit of the the Institute of Nuclear Sciences Applied to Health, University of Coimbra.

The main goal of the internship was to apply the knowledge acquired during the lecture component of the master's degree in Clinical Research Management and it centred on the activities of Clinical Trial Assistant and Start-Up Specialist in an academic environment.

The report included a literature review on clinical research, the panorama of clinical research in Portugal along with its regulations and a description of the importance of clinical research units. After, this work focus on the specifics of Clinical Research with Radiopharmaceuticals. The challenges of clinical research with radiopharmaceuticals are presented and possible opportunities for improvement in the area are discussed, with the aim of boosting the development of new radiopharmaceuticals and, consequently, their application in clinical practice. Finally, the activities performed as part of the curricular internship at CRU^{2}C are described.

In conclusion, the curricular internship acts as an essential tool for acquiring practical experience in clinical research management, contributing to the development of the skills needed to work in this area.

Keywords: Clinical Research, Regulation, Clinical Trials Unit, Radiopharmaceuticals.

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List of Abbreviations

API – Active Pharmaceutical Ingredient

AxMPs – Auxiliary Medicinal Products

CDR – Code of Federal Regulation

CEIC – National Ethics Committee for Clinical Research

CNPD – National Data Protection Commission

CRO – Contract Research Organization

CRU^2C – Clinical Research Unit University of Coimbra

CT – Clinical Trial

CT – Computed Tomography

CTD – Common Technical Dossier

CTIS – Clinical Trials Information System

CRF – Case Report Form

CRU – Clinical Research Unit

CTA – Clinical Trial Assistant

CTU – Clinical Trial Units

EANM – European Association of Nuclear Medicine

EEA – European Economic Area

eaIND – expanded access INDs

eIND – exploratory INDs

EMA – European Medicines Agency

EudraCT – European Union Drug Regulating Authorities Clinical Trials

FDA – Food and Drug Administration

FMUC – Faculty of Medicine of the University of Coimbra

GCP – Good Clinical Practice

GLP – Good Laboratory Practice

GMP – Good Manufacturing Practice

IAEA – International Atomic Energy Agency

IB – Investigator's Brochure

ICH – International Conference on Harmonization

ICNAS – Institute of Nuclear Sciences Applied to Health

IMP – Investigational Medicinal Product

IMPD – Investigator Medicinal Product Dossier

IND – Investigational New Drug

INFARMED – National Authority for Medicines and Health Products I.P.

ISF – Investigator Site File

MA – Marketing Authorisation

MRI – Magnetic Resonance Imaging

MS – Member States

MTD – Maximum Tolerated Dose

PD – Pharmacodynamic

PET – Positron Emission Tomography

PIP – Paediatric Investigation

PI – Principal Investigator

PK – Pharmacokinetic

QA – Quality assurance

QC – Quality Control

QMS – Quality Management Systems

RDRC – Radioactive Drugs Research Committee

RNCES – National Network of Ethics Commissions for Health

RNEC – National Registry of Clinical Studies

SDV – Source Data Verification

SmPC – Summary of Product Characteristics

SNS – National Health Service

SPECT – Single Photon Emission Computed Tomography

TRT – Targeted Radionuclide Therapy

Introduction

As part of the Master's programme in Clinical Research Management, students have the opportunity to take part in a curricular internship in a real working environment.

My internship occurred at the Clinical Research Unit of the University of Coimbra (CRU^2C), between October 2023 and May 2024, and helped me acquire and consolidate skills in clinical research management.

This report begins by describing Clinical Research, its scenario in Portugal, the current legal framework, and the importance of Clinical Trial Units.

This is followed by a presentation of the specifics of clinical trials with radiopharmaceuticals, their challenges, and possible opportunities for improvement. The choice of this topic is related to the activities carried out during the internship but also arises from the need to simplify the process of introducing new radiopharmaceuticals into clinical practice. Next, the objectives of the internship, the host institution, and the activities carried out during the internship are presented, including any deviations that occurred. Finally, the present work ends with a critical discussion and conclusions on the topic of the state of the art and the course of the internship.

Chapter I

Literature Review

1. Clinical Research

Clinical research is any systematic study or investigation conducted on one or more human subjects or based on individual health data, designed to discover, or verify the distribution or effect of health factors, health states or outcomes, health or disease processes, and the performance and safety of health interventions or services, through biological, behavioral, social or organizational aspects [1]. It aims to develop and gather knowledge by testing hypotheses and applying statistical methods to draw a reliable scientific conclusion, which is fundamental to improving patients' healthcare and quality of life. [2,3].

The successful implementation of clinical research methodology relies on numerous aspects, such as the type of study, objectives, population, study design, methodology, sampling, and statistical procedures [4]. The appropriate choice of study design is one of the most critical steps for the successful execution of clinical research because it has an impact on the quality, execution, and interpretation of the research. [5]

Clinical studies can be divided into non-interventional (or observational) and interventional clinical studies (experimental). [2,6]

Non-interventional Clinical studies are studies in which the procedures applied to the participants follow standard clinical practice. [7] These studies are also known as observational studies, where drugs or medical devices are prescribed according to standard clinical practice, rather than as part of pre-established study protocol. They encompass diagnostic procedures and patient follow-up to evaluate real-life products or procedures, including risk/benefit assessment and resource utilization. They adhere to usual clinical practice guidelines, ensuring consistency with typical clinical procedures, and are not defined by a protocol designed specifically for a study. They do not test medical intervention, such as a drug or device, but may help identify new treatments or prevention strategies to test in clinical trials. [1,8,9]

The observational studies can be divided into descriptive and analytical. Descriptive observational studies provide a description of the exposure and/or the outcome, and analytical observational studies provide a measure of the association between the exposure and the outcome. [2]

Descriptive studies only describe data on one or more characteristics of a group of individuals; Its focus is not on testing hypotheses but on answering specific research questions. However, it is important to note that a descriptive design is not able to provide answers to "why" questions.[7,10]. The researcher does not manipulate any of the variables but merely describes the sample and/or the variables. Although a descriptive study can explore multiple variables, it is the only design that can also explore a single variable.[10] These studies identify patterns and trends in a situation, but not the cause-effect link between its different elements. [11] These studies can involve the use of questionnaires, interviews, direct observation, or the use of databases. Descriptive data allows researchers to categorise and understand the scope of clinical or social phenomena, often providing the basis for in-depth research. [1]

Observational studies include case reports, case series, ecological studies, cross-sectional studies, cohort studies, and case-control studies. [2]

On the other hand, **Interventional Clinical studies**, or experimental studies, are defined as " any research that advocates a change, influence, or programming of the health care, behaviour, or knowledge of participants or caregivers, to discover or verify health effects, including exposure to medicines, the use of medical devices, the performance of surgical techniques, exposure to radiotherapy, the application of cosmetic and body hygiene products, physiotherapy intervention, psychotherapy intervention, the use of transfusion, cell therapy, participation in individual or group education sessions, dietary intervention, intervention in access to or organisation of healthcare or intervention designated as unconventional therapy" [1]. Interventions include, but are not limited to, drugs, biological products, surgical procedures and medical devices. These studies test hypotheses and the researcher controls the risk factor/exposure of interest/treatment during the study. [2,5] These studies are the primary way for researchers to determine if a new form of treatment or prevention is safe and effective in people. [8] Research methodologies, such as randomization and blinding, are frequent in these studies. [12]

In addition to the classifications presented above, studies can also be divided, according to their sponsor, into industry-initiated studies, or commercial studies, and investigator-initiated studies, or independent studies. These studies will be discussed later in this report.

Given its importance and risks, clinical research is subject to strict regulations and legislations to ensure the safety and well-being of the subjects and the reliability and robustness of the data generated in the clinical studies. According to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), they must be carried out by investigators qualified by education, training, and experience to perform their respective tasks for the proper conduction of the trial. The investigators should provide a current curriculum vitae and other pertinent documentation as proof of these qualifications. The study should be conducted in accordance with the protocol agreed to by the sponsor and by the regulatory authorities. It should adopt all the necessary ethical and legal measures and ensure that all the participants freely give consent to participate in the trial. These strict ethical guidelines ensure the equal recruitment of a diverse population, protecting against bias and guaranteeing the generalisability of research results across different demographic groups. [13,14]

1.1. Clinical Trials – Overview

Clinical trials are defined as "any investigation in human subjects intended to discover or verify the clinical, pharmacology and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy". [14]

Participating in a clinical trial implies that participants are involved in the research by adhering to a predetermined protocol designed to discover/evaluate the effects of health care interventions/on health outcomes. In addition, participants can access experimental treatments and their involvement becomes a valuable contribution to medical research, ultimately benefiting others in the search for advances in healthcare. [15]

Clinical trials involve ethical issues that correspond to the risks faced by the human participants, requiring careful assessment of the study's impact on participants and more stringent regulation. Those responsible for planning and carrying out these trials must balance between the potential benefits and the risks and burdens for the involved subjects. Although not all participants may benefit directly from the treatment under study, they can receive support and comfort through the careful monitoring of a qualified research team. [16]

1.1.1. Clinical Trial Phases

Clinical trials (CTs) are conducted in different phases. Each phase is designed to answer certain questions. The phases of drug development, I-IV, depend on the objectives and methodologies of the investigation, as shown in **Figure 1**. The general aim of a CT design is to be able to provide the best and most reliable possible estimates of the safety, and in the later stages, of the efficacy of the compound studied.[17]

Patients can access new medicines during clinical trials or when they are introduced on the market. At the clinical trial stage, early access to medicines is particularly important in the case of pathologies for which existing treatments are less satisfactory in terms of efficacy, safety or even maintaining quality of life. [18]

Drug development is a long and complex process that can take 10 to 16 years to be designed, developed, and approved for use in patients. This process includes the discovery phase, which covers basic research, target identification and validation, a pre-clinical research phase, in which drugs are subjected to laboratory (*in vitro*) and animal tests (*in vivo*) to assess fundamental safety issues, a clinical stage divided into three clinical phases, and the fourth and final trial phase represents post-marketing research. [17,19]

Pre-clinical studies play a crucial role in the transition from drug discovery to clinical trials. Carried out under good laboratory (GLP) and scientific practice guidelines, they aim to guarantee the reliability and reproducibility of the results [20] These studies can help identify a lead candidate from several options, optimise the scale-up procedure for the new drug, select the best formulation, and determine aspects such as route of administration, frequency, and duration of exposure, as well as support the design of the planned clinical trial [21] The animal studies aim to assess the safety of the drug at doses comparable to estimated human exposures, pharmacodynamics, and pharmacokinetics. [22]

Following the completion of pre-clinical development, the sponsors/investigator begin a sequence of CT following GCP standards, involving volunteer participants.

The concept of **First-in-human** is also widely discussed. First-in-human trials are pivotal in drug development, representing the first testing phase of experimental medicinal products on humans after prior evaluation through *in vitro* or animal testing, or through mathematical modeling. Typically, these trials involve administering low, sub-therapeutic single doses to a small group of healthy volunteers (usually 10 to 15 individuals). First-in-human trials serve to initiate the evaluation of an investigational medicinal product (IMP) in human beings, intending to assess its pharmacology, tolerability, and safety, while at the same time examining how the effects observed in non-clinical studies manifest themselves in human beings. [23]

While First-in-human trials are indispensable for medical progress, they entail risk to participants, often healthy volunteers, as researchers' ability to predict the effects of a new drug on humans before human trials is limited. Nonetheless, occurrences of serious harm to participants in these trials are exceedingly rare. [24]

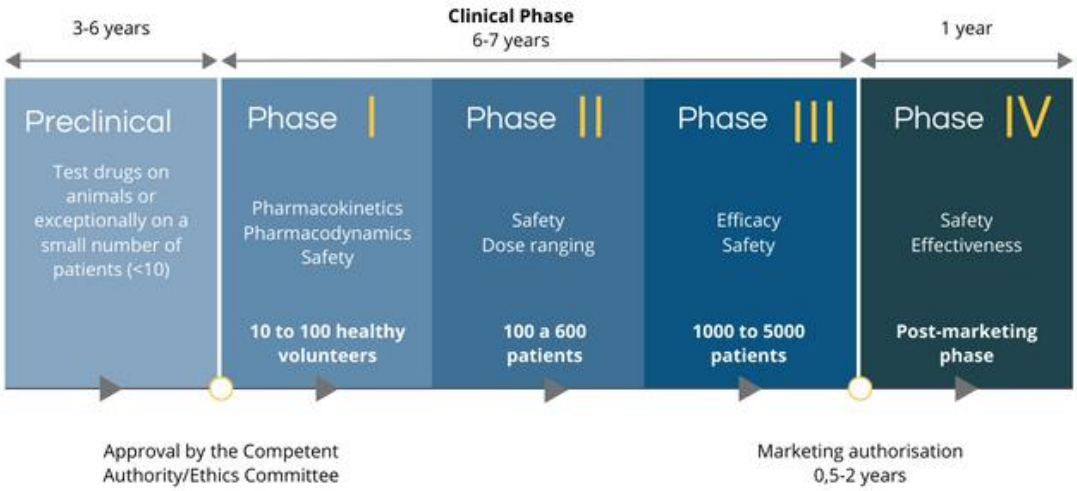


***Figure 1**. Phases of Clinical Trials*

Clinical trials are designed to prove both the safety, collected systematically, including surveillance for previously identified possible adverse effects, and efficacy of the drug. They are classified into four main phases [19,25] :

Phase I: Also known as human pharmacology studies, represents a key point in drug development, as it is the first time that the experimental drug is being tested on human beings. Therefore, it is essential to assess and identify the Maximum Tolerated Dose (MTD) and safety of the new compound. [26] They provide initial safety data that supports later tests with larger samples. Since the main objective is safety and not the efficacy of the treatment, these studies usually involve a small number of healthy volunteers. [25] However, in some cases, such as oncology, they can be carried out in restricted groups of patients. [27] Secondary goals include pharmacokinetic (PK) information (absorption, distribution, metabolism, and elimination), and effects on molecular targets or pathways (pharmacodynamics [PD]).

The assessment of potential adverse effects on participants is carried out throughout the clinical trials. The trial sponsor is also responsible for ensuring a thorough review of all pre-clinical data by experts with technical, scientific, and clinical expertise. [17]

Phase II: Once phase I has been completed, therapeutic exploratory trials commence, in which the IMP is tested for its safety in a wider population of individuals affected by the disease for which the drug has been developed [17]. These participants are selected based on strict criteria to form a relatively homogeneous group and are closely monitored. [27] Its aim is to investigate the use of the drug for the intended indication, determine the dosage for future studies and establish the basis for the design, parameters, and methodologies of confirmatory studies, like optimal doses, frequency of administration, routes of administration and other parameters. They also play an important role in evaluating potential trial parameters, defining therapeutic regimens, concomitant medication and identifying the target population, including age, gender, and disease stage. [17]

However, the small number of participants and primary safety concerns within a phase II trial usually limit its power to establish efficacy, and thereby support the necessity of a subsequent phase III trial. [22]

Phase III: Also referred to as therapeutic confirmatory studies, comparative efficacy, or pivotal trials, they are essential to prove the efficacy, therapeutic advantages, and safety profile of the new drug, to provide an appropriate basis for assessing the benefit/risk ratio and to explore the dose-response relationship. This phase is a crucial step to compare the new drug with the existing standard treatment or a placebo. Usually involving hundreds to thousands of patients, these studies are essential for obtaining a marketing authorisation (MA). [17,28]

The main goal of these trials is to validate the therapeutic advantages using important clinical endpoints, prioritising them over surrogate endpoints. They reinforce the initial evidence collected during the exploratory phase, confirming the safety and efficacy of the drug for a specific indication and population. These studies can also explore the effects in different populations and stages of the disease, as well as assessing the compatibility of the drug in combination therapies. [17]

Conducted with precision and control, these trials provide solid scientific evidence of the efficacy of the treatment after phase II. To be considered confirmatory, they must have clearly defined hypotheses before they begin, with sample sizes designed to detect benefits with statistical precision and exclude therapeutic ineffectiveness. Collecting safety data is crucial, as larger sample sizes in phase III studies offer a better ability to identify serious and potentially rare adverse events. [25]

Phase IV: Also known as therapeutic use or post-marketing surveillance trials, these studies are conducted after a medicinal product has been approved by the regulator for the market and distribution. They are conducted to assess the long-term safety and effectiveness of marketed drugs through the identification of side effects, toxicities, drug interactions and overall tolerance that may only emerge over time. [17,22]

The main objective of these trials is to evaluate the drug's real-world performance through continuous pharmacovigilance and provide essential technical support.

Although not mandatory for the marketing authorization process, these studies hold significance in gaining a comprehensive understanding of the new medicine's use. This includes assessing its impact on a patient's quality of life, identifying rare adverse events that may not have been detected in the smaller phase III studies due to the larger and more diverse population exposed, assessment of dose-response, optimizing usage, and determining the cost-effectiveness. [17,25]

After the successful completion of the clinical phases (phases I, II, and III), the subsequent steps involve meticulous analysis of the results and evaluation of the registration process. This evaluation is carried out by the national (INFARMED) and European competent authorities (European Medicines Agency (EMA)). These regulatory bodies rigorously assess the safety, efficacy, and quality of the medicine by analysing the complete dossier, which includes the results and relevant information from the quality, non-clinical studies and clinical trials carried out. [29]

1.1.2. The Importance of Clinical Trials

Clinical trials are fundamental in advancing medical knowledge and improving global patient healthcare, contributing to the development of innovative therapies.

The development of new medicines and the conduction of CTs provide a diverse set of direct and indirect benefits for the country's social and economic development (**Figure 2**). A collaborative study conducted by PwC and APIFARMA in 2013 details the clinical trial activity in Portugal to try to understand its importance in the Portuguese economy, identify the main obstacles to their progress and outline a set of recommendations to overcome the identified limitations. More recently, an updated version of this study was published in 2019 and pointed out the main benefits of the conduction of CT in Portugal. These benefits were further categorized into three distinct groups. [29,30]

Clinical trials offer many advantages for patients, healthcare professionals, and the economy.

Concerning the advantages for patients, they provide early and free access to promising new therapies, often representing a treatment possibility for patients with serious conditions, while contributing to to the development of innovative treatments for patients and to the progress of society. The results of the clinical trial will determine whether the treatment was effective and safe for all patients. In cases of rare diseases, where there are few or no treatments available, taking part in a clinical trial may be the only opportunity for patients to access a potentially effective treatment. In addition, participants in clinical trials undergo more frequent and detailed surveillance than during their regular medical consultations, which allows for a more comprehensive understanding of the evolution of their clinical condition [31]. During these trials, participants are monitored closely and more frequently than during normal clinical practice, allowing for a more precise understanding of the effects of the treatments being studied. Specific tests are carried out to monitor participants' progress. Once the clinical trial is complete, the data is analysed to determine the safety and efficacy of the treatment. Only after this assessment can the treatment be made available on the market to all patients who need it, on prescription. [31]

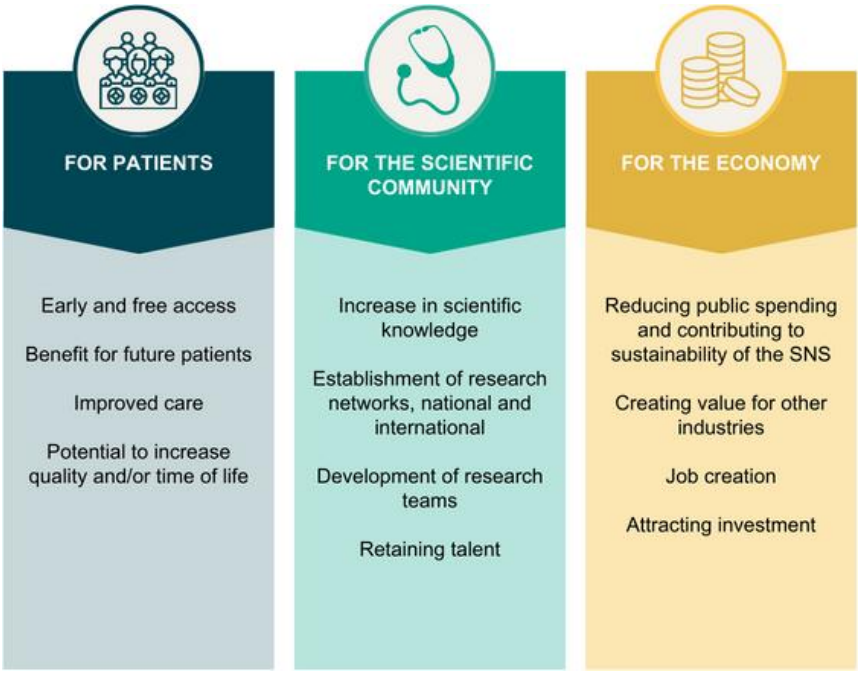


Figure 2. *Clinical Trials Benefits. Adapted from PwC*

For healthcare professionals, clinical trials offer opportunities to increase scientific knowledge, earn money and acquire skills in innovative technologies. The creation of national and international research networks also promotes the creation of jobs and centres of excellence, improving healthcare services.

Economically, clinical trials reduce public spending by financing treatments and diagnostics, as well as boosting the purchase of hospital goods and services, creating value for other industries. [29]

1.2. Portuguese Ethical and Regulatory Framework

1.2.1. Ethics in Clinical Research

For many years, research involving human beings was conducted with insufficient regulation, leading to various incidents and human rights violations. Because of these experiences, today there are strict ethical and legal regulations in this area, making it highly regulated. [32]

The **Nuremberg Code** [33], established in 1947 has served as a foundation for ethical clinical research. [34] This code made informed consent mandatory for all trials and emphasised that each individual must voluntarily consent to participate as a research participant. This means that the person must be legally able to give consent and be in a position to freely make their own choice without any form of coercion. One should fully understand the details of the subject matter involved to make an informed decision. Before agreeing to participate, one should be informed about the nature, duration, and purpose of the experiment, as well as the potential risks and effects on one's health. Those conducting the experiment are personally responsible for ensuring that the consent is valid and cannot delegate this duty to others. [34] In addition, the

code addresses the competence of the investigator, stipulating that research should only be conducted by scientifically qualified professionals. [11]

Similarly, in 1948, the **Universal Declaration of Human Rights** [35] highlighted the importance of respecting human dignity and preventing the mistreatment of individuals. [36]

With increasing advances in research, the Nuremberg Code was complemented by the **Declaration of Helsinki** [37], established by the World Medical Association in 1964, offering clearer guidelines for therapeutic and non-therapeutic research and serving as the basis for the ethical principles that guide the current good clinical practices guidelines. This declaration emphasized the need for written informed consent and the approval of research protocols by an independent ethics committee. It's revised time-to-time and the latest revision, in 2013, underlines the principle that standards of care in "developed" countries should be aligned with those in "developing" countries where trials are carried out. A working group was established in April 2022 to start another revision of this document. [36,38]

The Belmont Report [39] of 1979 was also an important guideline for the ethical regulation of the human experimentation.

In 1996, to overcome inconsistencies in the authorization process for new medicines in different countries, the ICH of Technical Requirements for registration of pharmaceuticals for Human Use issued the ICH Guidelines for GCP. [36,38] This document is a harmonized standard that is designed to protect the rights, safety and well-being of human subjects, minimize human exposure to investigational products/new drugs, speed up the marketing of new drugs and improve the quality of data [40]. Responsibilities of each participant of a CT, namely, the sponsor, the monitors, the investigators, the independent ethic committees and the regulatory authorities are described in this document.

Therefore, ethical principles are based on the four essential pillars of autonomy, beneficence, justice, and non-maleficence. More recently, two other important pillars have been incorporated: confidentiality and honesty. [32]

While there's a general agreement on the ethical Framework guiding clinical research, it's essential to recognise that each clinical trial possesses its unique characteristics. Therefore, a meticulous assessment of the protocol and methodology is necessary, along with continuous monitoring of the entire research process, always prioritizing the safety and well-being of participants. [27]

Every clinical trial carries a level of risk for participants, varying in magnitude. Adherence to GCP can mitigate these risks. This includes all internationally recognised precepts of ethical and scientific quality – which must be respected throughout all studies involving the participation of human beings, from their conception to their review, including their conduct, registration, notification, and publication. [27]

1.2.2. The Clinical Research Law No. 21/2014

Since 2004, the EU Clinical Trial Directive 2001/20/EC specifies the requirements for the conduct of clinical trials with medicinal products in the EU. As a directive, it is incorporated into the national legislation of each Member State, resulting in a complex structure for assessing multinational clinical trials. This directive was transposed into Portugal by the Law No. 46/2004, which only regulated clinical trials, later revoked by Law No. 21/2014 of 16 April, covering all research on human beings, including clinical trials with medicines, studies with medical devices, cosmetics, food supplements, and observational studies.[1]

Considering feedback from stakeholders, including the pharmaceutical industry, researchers, and patients, new legislation was enacted in 2014, the clinical research law (Law No. 21/2014) amended by Law no. 73/2015 of 27 July. [41]

The Law on Clinical Research aims to promote technological development in Portugal and strengthen health institutions through research. Its objectives include establishing a comprehensive framework for clinical research, regulating the processes for evaluating and conducting clinical studies, speeding up the approval of research to increase Portugal's international competitiveness, and generalizing the evaluation and registration processes for all types of clinical studies. [1]

This legislation introduces significant changes, including new comprehensive definitions, the regulation of all types of clinical studies, the inclusion of non-interventional studies, the reference to the National Data Protection Commission (CNPD), the establishment of the National Network of Ethics Commissions for Health (RNCES)). [1]

The law recognise the clinical and economic importance of clinical research. One of the changes is the creation of the National Registry of Clinical Studies (RNEC), an electronic platform coordinated by National Authority for Medicines and Health Products I.P. (INFARMED). RNEC aimed to register and publicise clinical studies underway in the country, facilitate the exchange of information during the process of authorising, monitoring and concluding trials, and increase access to and knowledge about these trials in Portugal. The main objective was to rationalise and streamline the approval processes for clinical studies, reducing the time needed for their evaluation. However, it currently only serves for notifications, submission of final reports and submission of studies with medical devices. [42]

1.2.3. European regulation No. 536/2014

At the time of its publication, Directive 2001/20/EC aimed to simplify and standardise the administrative provisions governing clinical trials in the European Union.

Three important aspects made the previous directive ineffective:

1) Disproportionate regulatory requirements;
2) High costs and a lack of harmonization of the applicable rules necessary for multinational clinical trials;

3) Significant decline in the number of clinical trials in the EU to which the restrictions imposed by the Directive had contributed. [43]

Practical experience has shown that the goal of fully harmonising the regulation of clinical trials has only been partially achieved with the directive. Taking the next step towards this harmonisation, Regulation 536/2014 of the European Parliament and the Council of 16th April 2014 on clinical trials on medicinal products for human use, replaces Directive 2001/20/EC, focusing exclusively on clinical trials of medicinal products for human use. [44] The regulation comprises 99 articles divided into 19 chapters along with 7 annexes and is immediately applicable and binding in all member states, without the need for it to be transposed into the legislation of individual states. [45]

The regulation was officially adopted by the European and published in May 2014. It became applicable on January 31, 2022. From January 31, 2023, onwards, all new clinical trials must adhere to the rules outlined in the CTR. For trials already running at the time of the regulation's application, a transition period of up to three years will be allowed. [46]

This new legal framework does not modify the scope established by the Directive, maintaining the same principles regarding the protection of the rights, safety, and well-being of trial participants. It also maintains an ethical approach and good clinical practice to guarantee the accuracy and reliability of the data produced.[47]

The primary objective of the regulation is to enhance Europe's competitiveness in clinical research, particularly in light of the decline in clinical trials in recent years. This is achieved through several key measures: [46]

1. Aims to simplify and harmonize the clinical trial approval process by setting deadlines and introducing a unified electronic submission system; [48]
2. The regulation encourages cooperation between EU member states to increase the efficiency of trials carried out in several countries, improving the use of resources; [46]
3. By reducing regulatory differences at national levels, the regulation aims to establish a coherent regulatory framework for clinical trials across Europe; [48]
4. Emphasis on producing high-quality scientific data through rigorous standards to ensure the safety of participants and the credibility of research; [46]
5. Promotes transparency by mandating greater disclosure of trial details, results, and methodologies, fostering trust and informed decision-making among researchers. [46]

Even with the implementation of this new regulation, in multicentre clinical trials conducted across multiple countries, the regulatory authorities of individual member states maintain the authority to approve or deny a particular clinical trial, even if it has obtained approval from another member state.

As previous mentioned, to simplify the procedures for submitting applications for the authorisation of a clinical trial and the duplication of mostly identical information, the regulation provides for the submission of a single application dossier to all the member

states concerned (where applicable), via a single portal, known as the clinical trials information system (CTIS). [49]

A crucial point addressed by the regulation is transparency in the dissemination of clinical trial data. EMA, in collaboration with Member States (MS) and the European Commission, has established an EU database (EudraCT) accessible through the CTIS to streamline and facilitate the exchange of information between sponsors and MS. EudraCT will contain a summary of trial results, accompanied by a simplified version for the lay public, which the sponsor must provide within one year of the end of the trial, regardless of the outcome. All details recorded in EudraCT will be made available to the public, except for personal information, confidential commercial data, confidential communications between Member States relating to the evaluation of the report, and information the disclosure of which could jeopardise the effective supervision of the conduct of the trial by the Member States. [45]

1.2.4. Submission Procedure

Before the Regulation, to obtain regulatory approval to conduct a clinical trial, sponsors of clinical trials had to submit applications individually to the national competent authorities and ethical committees in each nation. [50]

The CTIS appears as a single-entry point for the authorization, submission, and supervision of clinical trial data in the EU and the European Economic Area (EEA). The EU Member States and EEA countries are responsible for supervising and evaluating clinical trials in the CTIS, while the EMA establish and administer the platform. The European Commission ensures the accurate interpretation and application of the Clinical Trials Regulation. [51]

The CTIS has been designed with the following main features:

- Guarantee data confidentiality in the application process until a decision on the trial is made;
- Inclusion of relevant information about the clinical trial;
- Public availability of the database in an easily understandable format;
- Ability to link data and associated documents using the EU trial number and corresponding links;
- Functioning as a centralised platform for presenting data and information on clinical trials, with a focus on technical sophistication and ease of use to reduce unnecessary tasks. [50]

In Portugal, obtaining approval for a clinical trial application entails the submission to the following authorities:

- INFARMED is the competent authority responsible for the evaluation, supervision, and authorization of clinical trial
- National Ethics Committee for Clinical Research (CEIC) is an independent organization whose mission is to protect the rights, safety, and well-being of the participants in clinical trials, providing an ethical assessment of the research protocols. [1]

The evaluation report will have two sections: one focusing on the experimental product and the other on the wellbeing of the participants (ethics). Each Member State will make a unique final decision, although these sections may be presented together or in separate phases. [45] The Clinical Trials Regulation outlines detailed requirements for documentation and information needed for clinical trial applications, modifications, or additions in each Member State. [48]

Parts I and II of the dossier can be submitted together or separately. If submitted separately, Part I must be reviewed and approved before Part II can be presented. This separate submission allows for better handling of complex protocols, ensuring that design and acceptability are agreed upon before detailing peculiarities. [45]

Part I focuses on assessing technical, scientific, non-clinical, and clinical quality aspects. This evaluation is conducted by the "member state concerned" selected by the trial sponsor. [45,52] Annex I of the Regulation specifies the documents required for Part I, including a cover letter, clinical trial protocol, investigator's brochure, documentation on compliance with Good Manufacturing Practice (GMP), Investigator Medicinal Product Dossier (IMPD), Auxiliary Medicinal Product Dossier, copy or summary of any scientific advice of the EMA and Paediatric Investigation Plan (PIP), when applicable, labelling information for investigational medicinal products and proof of compliance with Union data protection laws. [45]

Part II addresses with intrinsically national aspects, like ethical aspects and local feasibility, such as patient information and informed consent, which are evaluated separately by each state and its ethics committees. It includes country-specific details like recruitment arrangements, suitability of the investigator or the Contract Research Organization (CRO), insurance coverage, financial and other arrangements, and proof of payment of the fee. [45]

The deadlines (**Figure 3**, **Figure 4**, **Figure 5**) for the assessment of dossiers requesting authorization for clinical trials should be sufficient to allow for the assessment of the dossier while ensuring rapid access to new and innovative treatments and ensuring the European Union remains an appealing place to conduct clinical trials.

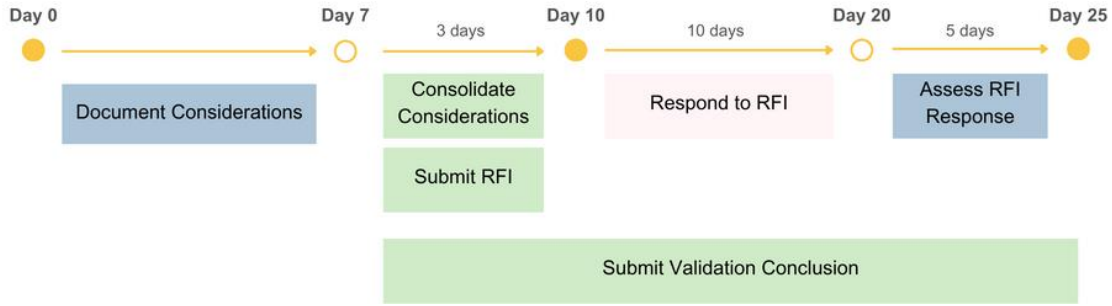


Figure 3. *Validation. Adapted from EMA* [53]

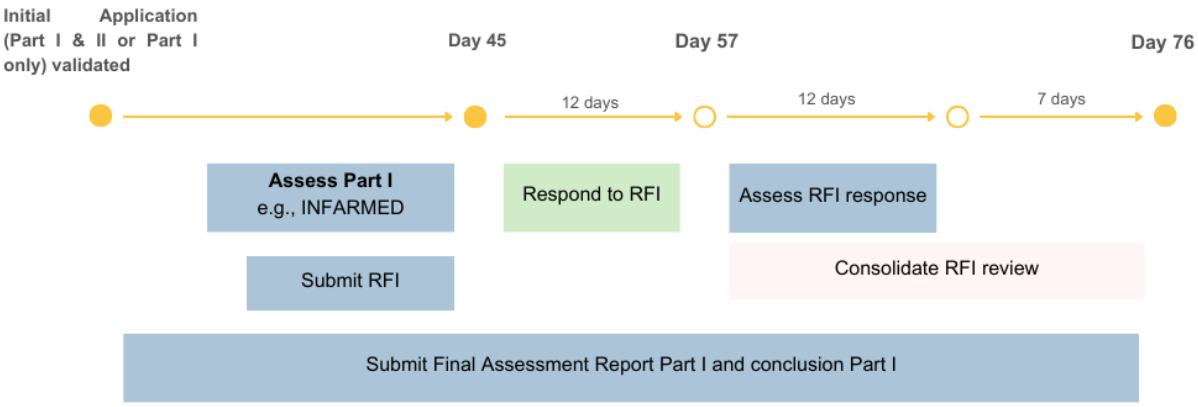


Figure 4. *Assessment Part I. Adapted from EMA* [53]

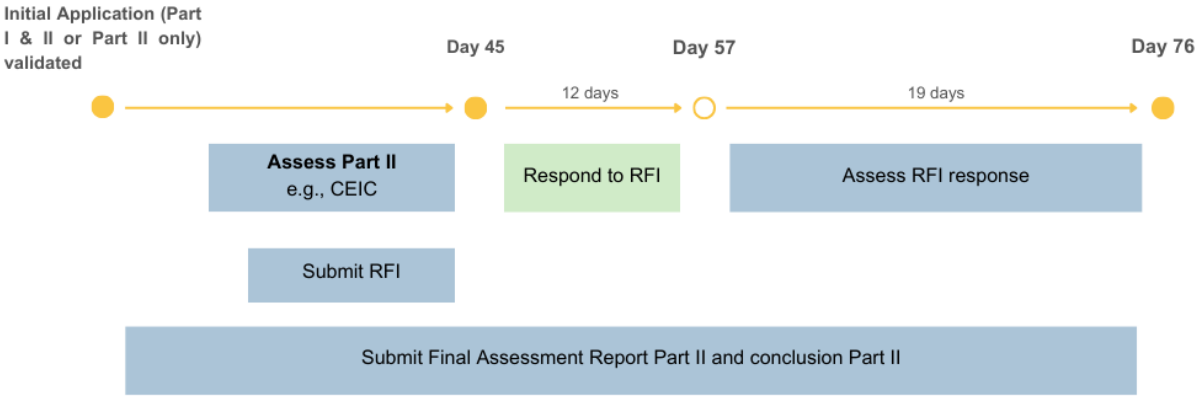


Figure 5*. Assessment Part II. Adapted from EMA* [53]

The notification must be made through a single decision, within five days of the date of the report or the last day of the assessment, if this date is later.

During the course of a clinical trial, changes may arise in the implementation, the design, the methodology, the investigational or supportive medicinal products, or the investigators or sites involved. If these changes are substantial, they must go through an authorisation process similar to the initial authorisation procedure.

1.2.5. Regulation (EU) No. 536/2014 vs. Law No. 21/2014

The law was created to implement the directive in Portugal, which is why it differs in some aspects from the current regulation. **Table 1** shows the comparison between the two documents for some main points.

Table 1. *Regulation/Law Documentation*

	Regulation (EU) No. 536/2014	Law No. 21/2014
Electronic submission	EU Portal and Database	National Clinical Trials Register
Public availability of information on clinical trials	EU Database	National Clinical Trials Register
Deadline for evaluating a submission begins	45 days (without request for additional information or documents)	30 working days (without request for additional information or documents)
Deadline for special cases	45+50 days for Advanced Therapies	45+20 days for: gene therapies; somatic cell therapy; experimental medicines containing genetically modified organisms
Deadline for evaluation by the competent authority and ethics committee of substantial changes	45 days (without request for additional information or documents)	20 working days (without request for additional information or documents)

The Clinical Research Law (Law no. 21/2014) and EU Regulation no. 536/2014 address crucial issues in a clear manner, offering defined answers:

- They set deadlines for the more efficient and harmonised evaluation of trials in all EU Member States; [1,49]
- Encourage efficiency and clarity in the evaluation and clarification processes; [1,49]
- Set legal deadlines for the approval of the financial contract by the administrative councils; [49]
- Create a legal framework for the transparent disclosure of clinical trials; [1,49]
- Provide clear instructions for promoting academic research. [49]

1.3. Clinical trial activity in Portugal

Despite witnessing a positive evolution in CTs, when compared with other European countries of similar size, Portugal still records the lowest number of recruited participants per million inhabitants, indicating significant potential for improvement. [54]

Over the years, Portugal's clinical research sector has witnessed a decline in its overall position in terms of health investment. This trend is contradictory given the significant benefits that research brings to patients, healthcare institutions, professionals, and the scientific community. Despite possessing outstanding scientific capabilities and skilled professionals, Portugal faces challenges in attracting crucial investment due to administrative obstacles. This annual loss of investment jeopardises the country's ability to promote competitiveness and slows down its development. [18]
The previously mentioned report discusses both the benefits of clinical trials in general and the major difficulties that Portugal faced in terms of their development and segments them into 5 dimensions. [29]

1.3.1. Challenges and Barriers to Clinical Trials in Portugal

Rising costs and administrative challenges have made Europe less attractive to clinical trial sponsors and researchers, especially academics. This is reflected in a drop in the number of clinical trials submitted, higher costs, and delays in starting these studies. In addition, there are fewer articles published on drug research in the region and a tendency for these studies to be carried out in other areas of the world. [47]

Portugal presents barriers in the **policy and strategy of the sector**, which originated from the lack of recognition of the strategic significance of clinical research, the absence of a development strategy, and the negative reputation surrounding clinical trials. [29]

Regarding **regulation and legislation**, obstacles include uncompetitive approval times for clinical trials, inefficiency, and lack of definition in the processes for requests for clarification, the absence of legal deadlines for approval of the financial contract, inadequate conditions for conducting trials in Health Centres, and the absence of a legal framework for clinical trial dissemination. Furthermore, financial contracts need standardized structures, and there's a deficiency in legislation promoting and regulating academic research. However, this dimension has been improved through the implementation of the new regulation. [29]

In terms of **organisation and infrastructure**, Portugal's strategic potential for clinical research is undervalued by hospital administrations, with health units primarily focused on a care-centric model. Research is often conducted sporadically and lacks dedicated support structures, while cooperation for research is insufficient. [29]

Challenges also persist in **career** development, **training, and support,** with inadequate financial incentives, minimal impact of research on professional growth,

insufficient academic and advanced research training; and limited opportunities for researcher-led initiatives. [29]

Lastly, in the **information and technology** area, Portugal faces obstacles due to the absence of a platform to promote and support clinical research, along with the failure to integrate systems across healthcare. [29]

Overall, there is a failure to recognise the critical role of clinical research in improving healthcare and strengthening the national economy and clinical research is not prioritised in the National Health Plan. [55]

APIFARMA has proposed solutions to meet the challenges, such as:

- Establishing a national organisation for clinical research;
- Standardising the necessary documentation;
- Developing trial sites with specialised management and appropriate infrastructure;
- Implementing strategies to improve recruitment and retention rates;
- Strengthen cooperation between key players;
- Regulate incentives for professionals involved in participating. [29]

Over the years, efforts have been made to strengthen activity in the areas of **Regulation and Legislation**, such as the implementation of the Clinical Research Law (Law no. 21/2014, of 16 April) and the regulation on clinical trials of medicinal products for human use (Regulation (EU) no. 536/2014), in **Policy and Strategy** with the creation of the Agency for Biomedical Research (AICIB) and where the creation of a single regulatory framework, directly applicable to all European Union Member States, best fulfils the objectives of generating a sufficiently competitive and more attractive European internal market in terms of clinical trials, although particularly orientated towards the development of pharmaceutical products and **Public Literacy** in Clinical Research through the dissemination of issues and publications such as APIFARMA. [47,56,57]

The creation of the Portugal Clinical Trials platform represents a significant step forward in the field of clinical research in Portugal. This platform plays a key role in promoting transparency by offering centralised and open access to the entire network of clinical trials carried out in the country. By providing detailed information on ongoing trials, the investigators, the institutions involved and the inclusion criteria for participants, the platform makes it easier for patients and healthcare professionals to find and take part in relevant studies. This not only raises awareness of the research opportunities available but also strengthens confidence in the integrity and quality of clinical trials conducted in Portugal. [58]

1.3.2. Evolution of activity

Clinical trials carried out in Portugal on the initiative of the pharmaceutical industry showed a dynamic growth between 2019 and 2022, increasing by 43 per cent. [59]

Clinical trials are a source of investment, attracting potential investors, such as international pharmaceutical companies, while at the same time promoting clinical innovation and attracting and retaining highly qualified human resources. Despite notable advances, Portugal has not yet implemented all the necessary measures to mobilize substantial growth in this field. [57]

Based on data extracted from the INFARMED statistics on the evaluation of marketing authorisations for medicinal products for human use, information was compiled for the last decade. **Chart 1** **Chart 1**shows the number of Clinical Trial Authorisations (CTAs) submitted and granted, as well as INFARMED's average decision time.

Concerning clinical trial authorization applications, the number of approved CTAs has shown minimal fluctuations over the last decade. However, there was an increase in authorised CTAs between 2020 and 2022.

It is important to highlight that in 2022 both the number of applications (230 in total) and the average decision time (87 days) reached their highest peaks. One possible explanation for this is the fact that many of the applications were suspended in 2020 to prioritise investigations into COVID-19, given the urgency of the situation at the time.

In terms of the average decision time (measured in working days), a positive tendency emerged from 2019 culminating in the lowest value recorded in 2020.

Due to the new regulatory requirements, there has been an increase in the submission of Clinical Trial Authorisation Applications to INFARMED over the last decade. **Chart 1** illustrates this trend, indicating that within a decade (from 2012 to 2022), the number of submissions (118 submissions to 230) has increased by approximately 95%, while the average decision time (40 days to 87) has risen to around 118%. [18]

It is noteworthy that the average decision time was lower in 2020 compared to the preceding year.

In 2014, the implementation of Portugal's new Clinical Research Law in Portugal was a significant step forward, coinciding with 127 requests for authorisation for clinical trials. This figure represents an increase of around 11 per cent compared to 2013. It should be noted that the average assessment time per clinical trial fell to 33 days, a 13 per cent reduction from the previous year.

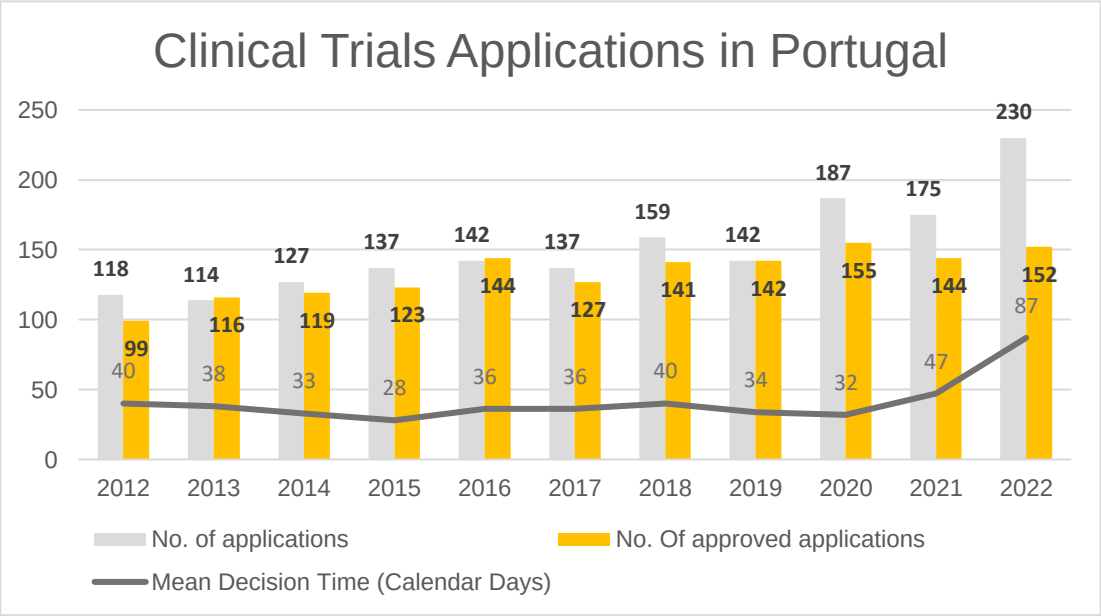


Chart 1. *Evolution of CTAs in Portugal. Source: INFARMED* [127]

Within the European context, Portugal stands out with one of the lowest numbers of conducted clinical trials, indicating a significantly smaller volume compared to countries of similar size, such as Belgium or Sweden. This discrepancy becomes apparent when assessing the ratio of clinical trials submitted per million habitants. For instance, with Portugal's population of 10.3 million, the ratio is 13.3, while Sweden (10.1 million habitants) and Belgium (11.3 million habitants) have significantly higher figures at 30.6 and 44.6 respectively, indicating considerable growth potential. [57,60]

While we have not yet achieved the desired level, Portugal is actively preparing the way forward. Action is needed across various domains, including the promotion of synergies between entities, the implementation of effective incentive policies, and proper recognition and valorisation of clinical research activity. In addition, taking advantage of technological advances is an opportunity to promote progress in this field. [57]

1.4. Clinical Trial Unit

Concerning sponsorship, clinical studies are typically divided into two categories: industry-initiated trials (commercial trials), which are sponsored by pharmaceutical or biotech companies, and academic or investigator-initiated studies (non-commercial trials), which are typically supported by non-profit organisations, such as independent researchers, academic institutions or study groups. [61]

Industry-initiated trials have historically led the promotion of clinical studies worldwide due to their advancements in technology, resources for conducting multinational trials, and utilization of global networks. The data collected from these multinational trials are crucial for the development and approval of new drugs as well as for validating treatment efficacy on a global scale, which is essential for improving healthcare systems in emerging economies. [61]

Investigator-initiated studies are conducted by researchers from non-pharmaceutical companies, which could include individual investigators, hospitals, institutions, collaborative study groups, or cooperative groups. They are also referred as Investigator Sponsored Trials non-commercial trials and Academic Clinical Trials. Investigator-initiated studies play a crucial role in addressing questions that typically arise after Phase III trials and have not been thoroughly explored during Phases I to III of drug development, like exploring new therapeutic uses, comparative effectiveness studies and cost-effectiveness evaluations. [62]

However, over the past decade, investigator-initiated trials have remained stagnant in most European countries, particularly those involving medicinal products. This stagnation can be attributed to the increasing burden of laws, regulations, and costs associated with clinical trials, making them more complex, time-consuming, and expensive. [61]

Despite the lower frequency of investigator-initiated clinical trials compared to those led by industry, the knowledge produced by these studies carries significant weight. This is primarily because they tend to address issues that are often ignored by industry-led efforts. Examples of these issues include the optimization of therapies, comparative analyses of treatments, proof-of-concept research, studies on orphan diseases, and paediatric trials, among others. In addition, these trials generate solid evidence, which is crucial for informing policymakers in making well-founded and sustainable decisions regarding public health policies, and contribute to the advancement of scientific knowledge, leading to publications in prestigious scientific journals with high impact factors (JIF). In addition, they play a crucial role in promoting the development of clinical teams, which is the foundation for creating a research site of excellence. [61]

Chart 2 compares the situation of these studies with those of the industry in Portugal.

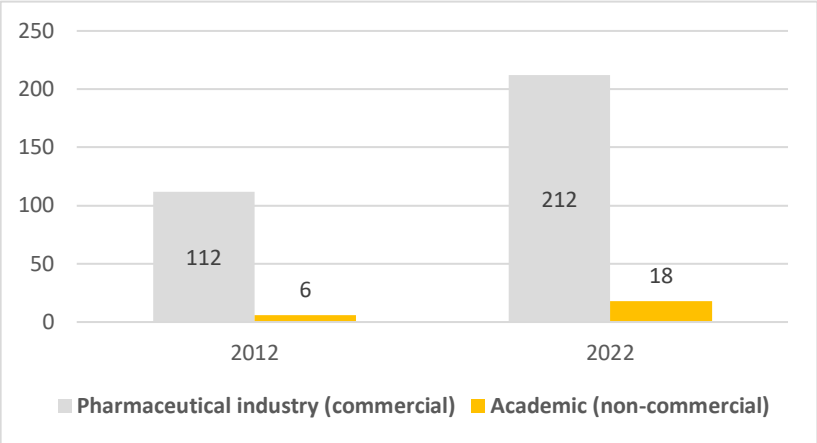


***Chart 2**. Number of active industry/investigator-initiated trials in Portugal. Source: INFARMED* [127]

Clinical Trial Units (CTUs) play a crucial role as sites of interdisciplinary expertise for clinical research in their local and surrounding academic institutions. Their main function is to efficiently support the clinical departments of universities and hospitals in the planning and execution of patient-oriented clinical research projects. Additionally, they significantly contribute to overcome the difficulty encountered in the previously mentioned APIFARMA report regarding the limited opportunities for investigator-initiated studies. [29] Fostering improvements in the quality of clinical research, CTUs address the growing need for support in various areas of study planning and conduct, while also raising awareness of the ongoing challenges at a national level. [63]

CTUs have to deal with several challenges and demands, including recruiting patients, staff rotation, regulatory compliance, and adherence to evolving standards of clinical research. Clinical Research in CTUs is a complex activity since operations usually involve a greater number of dynamic components compared to other healthcare sectors, requiring simultaneous attention to short and long-term objectives. [64]

In pharmaceutical industry-initiated clinical trials, investigators follow protocols set by the industry. However, in investigator-initiated trials, investigators and academic institutions or research units lead the process. They're in charge of designing the trial, getting approval from authorities, running it, and drawing conclusions. They also own the data and intellectual property rights. Despite meeting the same high standards, like following good clinical practice and laws, these trials often get less money and have fewer people working on them compared to those started by pharmaceutical companies. This makes them face significant challenges and disadvantages. [55]

In addition to the challenges faced in Portugal in the context of clinical trials, researcher-led clinical research activity faces problems of underfunding. [55] All these factors contribute to the fact that the number of clinical trials carried out in Portugal is low, especially concerning investigator-initiated trials.

The pharmaceutical industry invests in studies conducted by independent investigators from public institutions or research sites. However, this funding is conditional on the direct interests for the industry. For example, clinical trials that are not aimed at increasing the use of medicines may not receive funding, even though they are crucial for public health. [55]

Public funding is essential for carrying out studies that are independent of the pharmaceutical industry. These studies focused on patients rather than profit and are vital for advancing public health. Despite their importance, independent studies face challenges, such as a lack of resources, financial constraints, inadequate infrastructure, lack of clinical research training, and complex regulations. [55]

Chapter II

The Specifics of Clinical Research with Radiopharmaceuticals

2. Radiopharmaceuticals

Each year, over 30 million patients receive diagnoses or treatments through nuclear medicine and molecular imaging techniques. [65] Nuclear medicine uses radiopharmaceuticals to gain insight into the biological and molecular processes. Radiopharmaceuticals are drugs that contain two main components: a radionuclide/radioactive component for diagnostic and therapeutic purposes and a pharmaceutical component for localization in a specific tissue or organ. [66] The schematic design is shown in **Figure 6**. Similar to the development of new molecular entities that need druggable targets, the creation of novel radiopharmaceuticals demands a “traceable” target. [67]

These tracers are characterized by their tracer amounts (typically in the nanogram to microgram range), lack of pharmacologic effects, low incidence of side events, and short shelf-life. This combination of these characteristics makes radiopharmaceuticals crucial for various applications in medicine. [68]

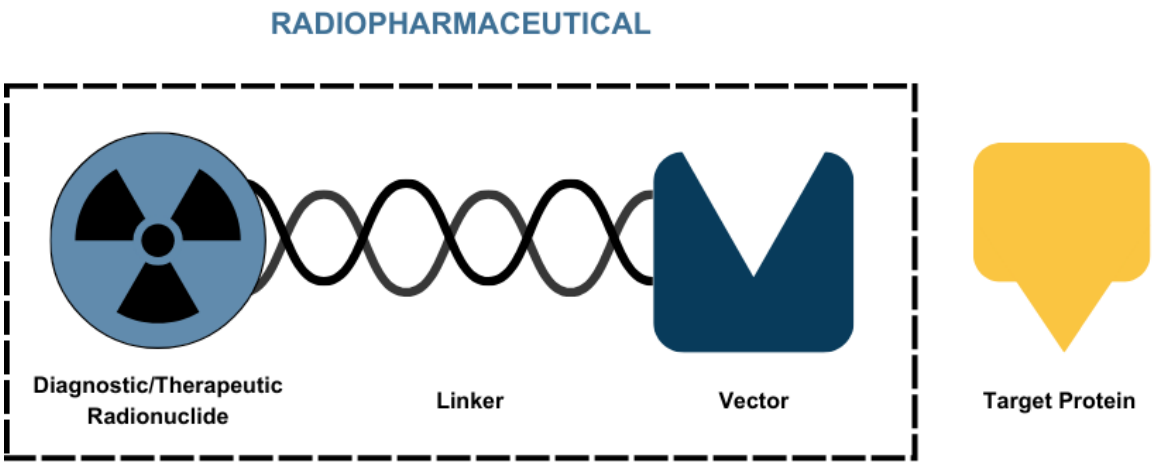


Figure 6. Schematic design of a radiopharmaceutical. Adapted from Dhoundiyal [81]

The characteristics of the two components determine the efficacy of the radiopharmaceutical. When developing a radiopharmaceutical, the first thing to choose is its preferential localisation in a particular organ or its involvement in the organ's physiological function. [69]

Radiopharmaceuticals are classified as medicinal products and their manufacturing, indications, and utilisation are regulated accordingly. [70]

Radiopharmaceuticals are classified into two categories based on their application: diagnostic and therapeutic. [69] The decay properties of the radionuclide determine if the radiopharmaceutical can be used for diagnostic or therapeutic purposes. [71]

2.1. Diagnostic radiopharmaceuticals

Diagnostic nuclear medicine imaging provides functional information at both molecular and cellular levels on several medical conditions. This non-invasive technique serves as powerful tool, offering unique information on physiological and biochemical processes. It is a complement to other imaging modalities, such as magnetic resonance imaging and computed tomography (CT). It is also capable of providing information at a cellular level that reflects the local biochemistry of diseased or damaged tissues. [72]

A radionuclide is marked on the selected pharmaceutical, allowing a radiation detector to identify the emitted radiation following its administration. This makes it possible to evaluate the organ's physiological function. The radionuclide is chosen according to the biological half-life of the active substance. [73] The pharmaceutical selected needs to be safe and non-toxic. The selection of the active substance, radionuclide, radiolabelling approach, and preclinical testing are all crucial factors in developing a diagnostic radiotracer. Once the radioisotope present in radiopharmaceuticals emits radiation for imaging, it's important that the radiation dose to the patient is kept as low as possible. [69] [74] This is because diagnostic radiopharmaceuticals are usually used at extremely low dosages that are not expected to have any side effects. Furthermore, the short lifetimes and low emission profiles of many diagnostic radioisotopes result in a comparatively low dosimetry. [73]

This modality plays an important role in the identification and management of diseases such as tumors, neurological and neurodegenerative disorders, and inflammation, and bacterial infections. [75] Its high sensitivity and specificity confer a significant advantage, allowing for early disease detection, monitoring of progression, precise staging, and provision of predictive information regarding the potential success of alternative therapeutic interventions. [72]

Nuclear medicine predominantly uses two robust, established imaging modalities: single photon emission computed tomography (SPECT) and positron emission tomography (PET). [76]

In Clinical practice, it's vital to ensure high performance and minimise scan time, often leading to the preference for short static scans. To achieve an adequate target-to-background ratio within the radionuclide's limited timeframe, there needs to be a sufficient interval between radiotracer injection and scanning. [67]

2.2. Therapeutic radiopharmaceuticals

In recent years, there has been a remarkable expansion in the field of therapeutic nuclear medicine. Beta-particle emitters and alpha-particle emitters are currently undergoing clinical trials. The radiation emitted by radionuclides, which accumulate in the tumour or in its microenvironment, can be used to target and eradicate cancer cells. The localization of tumours is achieved exclusively through target molecules, achieved through peptides or small molecules that adhere to receptors exclusively expressed in tumours, or through passive accumulation driven by physiological mechanisms. [77] Targeted radionuclide therapy (TRT) is usually administered systemically, delivering radiation directly to the tumour via the bloodstream, minimising damage to surrounding healthy issues. [23] Target molecules such as microspheres, nanoparticles, antibodies, peptides, and small molecules have been investigated. [77]

The advantage of this therapy lies in its ability to deliver a high dose of radiation specifically to the tumour while minimizing damage to surrounding healthy tissues, ultimately improving patient outcomes and quality of life. This targeted approach is particularly beneficial for treating systemic malignant tumours like bone metastases, where conventional external radiotherapy is not feasible, thyroid and neuroendocrine cancers. [77] Compared to chemotherapy, targeted radionuclide therapy is less invasive and requires a shorter treatment duration.[78]

For oncology therapeutic radiopharmaceuticals, it's essential to ensure they are specific, selective, and effective against tumours in patients who will benefit from the treatment. [79]

An innovative approach that is increasingly being explored and studied in cancer treatment is theranostics. Theranostics is an innovative strategy where the same radiotracers used for imaging can be adapted to treat diseased cells, thus integrating the two areas of therapeutics with diagnostics. [80,81] The location of the radiopharmaceutical can be visualised using a SPECT or PET scanner, and the standardised uptake value is used to quantify the amount of radiopharmaceutical in each region of the body. These images make it possible to identify and stage the target for diagnosis, select patients whose tumours express the target, confirm therapeutic delivery to all the intended targets in a patient, calculate the effective radiation delivered to the target (i.e., dosimetry) and monitor follow-up treatment. [82]

Theranostic treatments, such as Lutetium-177 (^{177}Lu)-PSMA-617 for prostate cancer, ^{223}Ra-dichloride for osseous metastases, ^{177}Lu-DOTATATE for neuroendocrine tumors, ^{131}I for thyroid cancer, and several others that are under development, offer improved diagnosis and reduced side effects compared to traditional methods. [80,83]

The major advantages of this approach include improved diagnosis, reduced adverse effects, simplified procedures, and better patient care.
Despite these advancements, further research is needed to understand how theranostic molecules work in human cancer and to develop improved agents. The increasing development of specific radiopharmaceuticals is changing clinical research

and management practices, leading to a greater demand for controlled clinical trials.[43,80]

2.3. Radiopharmaceuticals in clinical trials

In Europe, radiopharmaceuticals are considered a special group of medicinal products. Thus, their preparation and use are regulated by several EU directives, regulations, and rules that have been adopted by member states. So, firstly it is important to understand the differences between these concepts. [84] [68]

- Guidelines are not mandatory but serve as recommendations for Member States to effectively implement EU Directives. [85]

- Guidances are not mandatory but recommendations in a more specific and detailed form for the effective implementation of Directives by Member States. [85]

- Regulations are mandatory in all EU countries, as they are directly enforceable without the need for translational into national legislation. [85]

- Directives are rules sent by the EU Commission to Member States, which must then be transposed into corresponding national legislation and effectively implemented. [85]

Until 2014, the transposition of the directive into national law in the different EU member states led to significant legal variations across Europe. This created great obstacles to conducting clinical trials, the imposition of highly demanding and expensive regulatory requirements, a substantial decrease in investigator (rather than industry) driven studies, and an extremely slow pace for implementation of trials in practice. [43]

As the number of clinical trial applications decreased, the European Commission took action by initiating a revision process, leading to the implementation of Regulation (EU) No. 536/2014. Notably, this new regulation explicitly acknowledged the specific requirements for radiopharmaceuticals. [86]

As previous referred, the Regulation focuses on patient safety and reasonable and proportionate risk assessment, simplifying approval procedures that will also facilitate multicenter trans-national clinical trials with the creation of the centralised EU submission Portal, which will consequently facilitate and harmonize the application for clinical trials authorisation. [43]

Additionally, this regulation shift is expected to facilitate the assessment carried out by regulatory authorities and improve public access to information regarding clinical trials. [43]

On balance, it will have taken nearly two decades (2001–2020/23) to amend the laws that are necessary to conduct human subjects research and, as a result, improve patient care. It would require the implementation of much faster and more efficient procedures in the EU to react to the constant evolution of the development of medicines in general and radiopharmaceuticals in particular. [43]

The new Regulation introduces substantial changes in the field of **diagnostic radiopharmaceuticals**. There are three relevant points regarding the preparation of radiopharmaceuticals for clinical trials:

1) Authorisation is not necessary for the manufacturing of diagnostic investigational radiopharmaceuticals to be used in hospitals or clinical centres participating in the same clinical trial within the legally authorised in Member State concerned. This simplifies the production of diagnostic radiopharmaceuticals when used as IMPs in clinical trials. [43,71]
2) According to article 63(2) of the regulation, GMP production is not obligatory for diagnostic radiopharmaceuticals, even in the case of IMPs although it may still be mandated by local regulations. [43]
3) Simplified labeling of diagnostic radiopharmaceuticals used as IMPs or auxiliary medicinal products (AxMPs) [43]

It is important to consider that therapeutic radiopharmaceuticals do not have any special treatment in the new regulation and are considered in all respects in the same way as any other medicinal product used in a clinical trial. [43]
Therefore, EU regulation 536/2014, which is mandatory in EU member states, attempts to facilitate the experimental use of diagnostic radiopharmaceuticals, particularly concerning GMP criteria. [71]

For the first time, the regulation recognises that radiopharmaceuticals are special which is a major advance on current legislation. The regulation does not, however, reduce the type of documentation required for submission, so additional guidance on requirements for new radiopharmaceuticals needs to complement this process. [43]

Considering the specificities and characteristics of radiopharmaceuticals, some essential aspects have been consolidated to guide the conduct of clinical trials involving these substances.

Regarding the type and planned use of radiopharmaceuticals in a clinical trial, various scenarios could arise:

– Licensed radiopharmaceutical products used within their authorised indications

– Licensed radiopharmaceutical products used outside their authorised indications

– Radiopharmaceuticals with a proven clinical application that are made in compliance with regulations and quality standards that have been approved (e.g., as described in a pharmacopoeia monograph)

– New radiopharmaceuticals or tracer agents outside the previous categories.

As previously mentioned, clinical trials usually involve four phases, although phase IV studies usually do not apply to the radiopharmaceuticals under investigation. [87] While distinctions between these phases are not always clear, and opinions on details and methodologies may vary, each phase in the development of a radiopharmaceutical can be summarised as follows:

Phase I: Often performed on healthy volunteers, these are the first clinical studies for new radiopharmaceuticals. They aim to obtain preliminary evaluation of safety, as well as an initial pharmacokinetic and pharmacodynamic profile, and an initial safety assessment of the active ingredient and radiation dosimetry. [87]

Phase II: The aim of phase II studies is to establish activity and assess short-term safety. The trials are carried out on a limited number of subjects, but more than in phase I, and are designed to determine the optimum dose administered. The objective in the case of therapeutic radiopharmaceuticals is also to clarify dose-response relationships to provide an ideal context for the design of extended therapeutic trials. [87]

Phase III: Here, the trials are already involving large (and possibly varied) groups of patients to evaluate the therapeutic benefit of the intended radiopharmaceutical as well as the short- and long-term safety and efficacy assessing the overall and relative accuracy of the diagnosis. These studies are frequently multicentric. Along with looking into the special qualities of the product, we should also investigate the pattern and profile of any common adverse responses. In most cases, the test conditions should be as close as possible to the normal conditions of use. [87]

In recent years, the Phase 0 trial emerged as an intermediate stage between the preclinical and Phase I stages. In this phase, low doses (subtherapeutic) of an experimental drug are administered to a relatively small group of volunteers. [17]

These trials have the potential to enhance the selection of preclinical candidates by employing approaches, such as subtherapeutic microdosing, providing *in vivo* human data on pharmacokinetics, pharmacodynamics, and target engagement earlier in the development process than traditional methods. [88]

Although not widely practiced yet, these trials have the potential to become important tools in studying crucial aspects of human pharmacology during the final stages of preclinical development. The primary goal of these studies is not to provide therapy, but rather to evaluate human toxicology. Since participants receive doses below the therapeutic level, the risk of adverse reactions is lower than in conventional Phase I trials. [17]

Moving from preclinical investigations to clinical implementation, where the radiotracer transitions into a radiopharmaceutical, involves overcoming various regulatory obstacles. Guidance on the nonclinical safety studies required before initiating human trials can be found in ICH M3 R2.1. [67]

2.3.1. Challenges in Radiopharmaceutical Clinical Trials

The varying regulations across different countries pose obstacles to the expansion of the dynamic radiopharmaceutical fields. The International Atomic Energy Agency (IAEA) has been addressing this challenge through diverse initiatives. The challenges faced in testing radiopharmaceuticals are outlined below. [89]

Production

The production of a radiopharmaceutical involves three main steps:

1. Production of the radionuclide
2. Incorporation of the radionuclide with the non-radioactive compound to obtain the radiopharmaceutical
3. Purification and reformulation.

In the case of diagnostic radiopharmaceuticals, minimizing production time is essential to prevent activity loss due to decay during the production process. [67]

Professional organisations, such as the European Association of Nuclear Medicine (EANM), have provided a guideline and a guidance document dedicated to small-scale radiopharmaceutical production. [90]

Quality Control

Quality control procedures play a fundamental role in guaranteeing the quality of all radiopharmaceuticals. These procedures include assessing the chemical, radiochemical, radionuclide identity and microbiological purity of radiopharmaceuticals. [23] It is crucial to establish the quality control process quickly to prevent any loss of activity in the radiopharmaceutical due to decay. [90]

As mentioned earlier, the new Regulation establishes that the preparation of radiopharmaceutical IMPs does not require a specific GMP authorisation for the process in specific cases. However, this exception is only valid if national regulations allow it and restrict its application to diagnostic purposes only.[90]

Several documents offer recommendations for the preparation of radiopharmaceuticals on a small scale, providing guidelines for these practices, including in the context of clinical trials. All these documents provide information on how a quality system should be applied in the preparation of small-scale radiopharmaceuticals. [90]

Documentation

Radiopharmaceuticals are not exempt from the usual preparation of documents. To progress to the first clinical assessment, a clinical trial application must be prepared and submitted for review by the local ethics committee and competent authorities. In the European Union (EU) this application includes the Clinical Trial protocol, IMPD, Investigator's Brochure, the informed consent form (ICF), and the case report form (CRF), to ensure that the trial is conducted in accordance with GCP and compliance with regulations and legislations. [67,90]

The key information regarding the radiopharmaceutical planned for the study can be found in the IMPD. The content follows a standardised format, known as the Common Technical Dossier (CTD), used in marketing authorization applications. This documentation contains information about the production, quality control, and

separates chemical and pharmaceutical data (Quality) from the non-clinical and clinical safety and efficacy information, covering the toxicology and pharmacology of the new radiopharmaceuticals. This division is crucial for radiopharmaceuticals. Consequently, EANM has issued specific guidance on designing an IMPD for radiopharmaceuticals, serving as a valuable reference for managing this task. [85,86]

In the specific case of radiopharmaceuticals, the easiest scenario for their use in a clinical trial is when they are already licensed. In this case, the Summary of Product Characteristics (SmPC), which replaces the Investigator's Brochure, is usually sufficient for the authority. [90]

The IMPD addresses the chemical and pharmaceutical **quality** of radiopharmaceutical, comprising two main parts: the drug substance (also called the active pharmaceutical ingredient, or API) and the final drug product (or finished product). [90] Radiopharmaceuticals differ from traditional pharmaceuticals in that they lack a final "active" ingredient as the radioactive component is integrated into the precursor molecule during synthesis. Consequently, they can't be characterised like a regular API. This uncommon situation can lead to difficulties in describing the product in this context. The EANM has therefore published a specific guideline detailing how to prepare a "radiopharmaceutical" IMPD.[90]

Translating pharmacokinetic data into dosimetry is crucial, although toxicity data for both radioactive and and non-radioactive materials must be provided. [90]

The European Pharmacopoeia is valuable for quality assessment and is recognised by all EU Member States. It's recommended to follow its monographs for established radiopharmaceuticals, with justification for any deviations and validation data for alternative quality control methods if needed. Even for new radiopharmaceuticals in clinical trials, referencing the pharmacopoeia, particularly monographs of similar radiopharmaceuticals, is advisable. Additionally, the pharmacopoeia provides useful monographs and general texts for quality criteria and analytical tests. [90]

Small-scale radiopharmacies face challenges in this document for clinical trials involving radiopharmaceuticals. One of the problems involves its structure, which is unsuited to the unique properties of radiopharmaceuticals, in addition to the enormous amount of data that must be compiled. Despite the regulatory changes that have been imposed, the need to prepare an IMPD as part of the application process for clinical trial authorization remains. [85]

Other challenges faced by smaller studies in seeking clinical trial authorization include:

1) The prerequisites are the same for both large trials by pharmaceutical companies and those by universities or hospitals.
2) While certain radiopharmaceuticals are documented in the European Pharmacopoeia, only a limited number of them are officially registered products. Consequently, even if a radiopharmaceutical has demonstrated its efficacy and safety through years of clinical use, it often falls under the category of IMP.

3) Due to the tracer amounts injected and the results of the risk assessment analysis, radiopharmaceuticals have an excellent safety profile, but this fact is still not widely appreciated.
4) Compliance with regulatory standards in clinical trials requires the generation of extensive documentation, with the IMPD constituting the majority. Thus, it becomes clear how the combination of the mentioned problems may compromise the standing of European research institutes in the field of radiopharmaceuticals. [85]

Pre-clinical data requirements

A set of experimental investigations must be conducted during the preclinical phase to corroborate the anticipated *in vivo* performance of the product in humans. These investigations involve *in vitro* tests to elucidate or validate potential mechanisms of action of the radiopharmaceutical, along with *in vivo* animal experiments to establish its pharmacological and toxicological profile. [89] The non-clinical safety studies required for pharmaceutical products are described in a specific ICH guideline, M3(R2).

In vitro tests are crucial for establishing the viability and mode of action of new radiopharmaceuticals before they can be tested on humans. The demonstration of specific accumulation in the target and the validation of the predicted mode of action provide the necessary basis for moving on to more complex *in vivo* studies and, eventually, clinical practice. [90]

In vivo studies with animal models are crucial for determining dosimetry estimates for the radiopharmaceutical, which guarantees its safety, biodistribution, dose escalation, pharmacokinetics, where efficacy is assessed, pharmacodynamics, or *ex vivo* analysis. [89] The data derived from these studies can be used instead of carrying out specific experiments. Currently, small animal imaging data is replacing traditional biodistribution data and, when planned correctly, imaging can provide dosimetry information, which reduces the number of animals used, in line with regulatory guidelines. [90]

Due to the unique characteristics of diagnostic radiopharmaceuticals - specifically administration in microdoses and the absence of a pharmacological effect - the general considerations of the ICH (M3) guideline are not always appropriate. It is important to adapt pre-clinical and regulatory requirements to reflect these differences, ensuring patient safety without requiring unnecessary studies that do not apply to the specific use of these radiopharmaceuticals. [89]

Radiopharmaceuticals are a special class of drugs composed of two components, one “cold” or non-radioactive (e.g., antibody, peptide) and one radioactive (e.g., fluorine-18, gallium-68, iodine-131). Thus, the toxicity of radiopharmaceuticals may be driven by the non-radioactive as well as the radioactive component. [23]

Unlike the other pre-clinical studies, **toxicity** studies for non-radioactive substances used in clinical trials must adhere to strict ICH guidelines. Extensive animal testing is necessary before starting clinical trials to ensure the compound’s safety. [90]

Toxicity testing for the non-radioactive compound involves a single dose study on a single animal species, usually rats, to evaluate chemical and histological effects. These studies must comply with GLP, which generally requires the involvement of specialised companies, which can increase costs. [90]

Another challenge is determining the dose based on mass, which can be problematic for radiopharmaceuticals with high molecular weights. The EANM has published a document addressing these considerations to assist in the process of translating new radiopharmaceuticals. [90]

The new microdose approach has been proposed as a powerful complementary tool to the existing methods, offering a simpler process. This approach assumes that important pharmacokinetics parameters of a new chemical entity developed as a drug can be assessed using very small doses (microdoses) of the investigational compound. Since these low doses are unlikely to produce pharmacodynamic effects or significant side effects after a single dose, it may be possible to conduct these studies in humans without the need for classical toxicology studies at therapeutic effective doses, as typically required before regular phase I trials. [23]

Although it's known that results from non-clinical studies may not perfectly translate to humans due to physiological differences, they still give a good idea of what to expect in terms of drug behaviour and safety. [89]

When it comes to developing radiopharmaceuticals, investigators and regulators often rely on guidance meant for non-radioactive drugs, which may not fit their needs well. This can lead to uncertainty in study design and the risk of gathering unnecessary or redundant data. [89] Another significant issue is the lack of a clear and consistent regulatory framework for radiopharmaceuticals. This makes it hard for both regulators and investigators to find the right information for study design. [89] To address these issues, investigators are advised to talk to regulators early on about their specific trial plans. While this approach works well in some places with strong regulatory systems, it's still a challenge in regions where regulatory communication is less developed. [89]

Actions taken and potential solutions

Recently, many entities have provided support for the necessary documentation in clinical trials involving radiopharmaceuticals. The European Commission issued a guidance document on dosimetry to categorise risk in medical and biomedical research based on effective administered doses. [89]

In 2018, EMA developed the "Guideline on Non-Clinical Requirements for Radiopharmaceuticals". This guideline addresses the non-radioactive component of radiopharmaceuticals and evaluates their pharmacological and toxicological effects. It is recognized that the main risks of radiopharmaceuticals are related to radioactivity, requiring different methods, especially in dosimetry. [89]

One of the goals of these guidelines is to reduce dependence on animal experiments, seeking a more adaptable regulatory framework, considering the unique characteristics of radiopharmaceuticals. [89]

As noted throughout the report, the planning and execution of clinical trials in Europe require meticulous care and involve substantial financial resources, especially those from investigator-led initiatives. To support these efforts, the European Union has established specific resources that provide funding for conducting clinical trials, including the utilization of research facilities. [90]

Major universities and hospitals have established clinical trial units to assist in planning and, to some extent, in the execution of trials, providing guidance on GCP and study monitoring. When trials involve multiple sites, it may be beneficial to engage a CRO to coordinate the trial on behalf of the sponsor. [90]

Scientific guidance is essential for therapeutic radiopharmaceuticals needing higher doses and repeated use in clinical trials. However, it's crucial to recognize that this guidance comes with a cost and is valuable only when the question is well-defined. Unlike diagnostic radiopharmaceuticals, therapeutic ones must comply with GMP standards, requiring more financial resources. Careful planning can help manage resources and seeking advice from authorities can ensure the acceptability of generated data for clinical trial applications. [90]

Other strategies to enhance the conduct of trials with radiopharmaceuticals include keeping in mind the following aspects:

- **Quality assurance:** Radiopharmaceuticals designated for humans cannot be prepared or dispensed without a strong quality assurance (QA) system. [85]
- **Time and cost-effectiveness of replication studies:** In cases where the biodistribution, dosimetry, and safety profiles of specific radiopharmaceuticals are well documented in international peer-reviewed journals and their clinical value is established, using this existing data can accelerate the introduction of new radiopharmaceuticals into clinical practice. This approach offers immediate advantages by avoiding redundant pre-clinical, phase I and II studies, leading to significant savings in time, resources, and costs for the benefit of patients. However, adherence to local regulations governing the manufacture and use of radiopharmaceuticals is crucial. Some countries may require the generation of local data to validate the product, but repeating phase I, II, and III studies may be unnecessary if there is already consistent, literature-supported data on the use of the radiopharmaceutical. [85]

When evaluating a new radiopharmaceutical, it is crucial to consider its pros and cons to optimise cost and time efficiency and increase the likelihood of positive results. The success of a radiopharmaceutical depends on factors such as clinical utility, demographic relevance, payment considerations, acceptance by referring physicians, access to imaging resources, reporting capabilities, and the presence of a dedicated clinical leader. [85]

Given that planning is the foundation for the success of these trials, the following sequence of steps (**Figure 7**) is proposed to introduce a radiopharmaceutical into clinical practice.

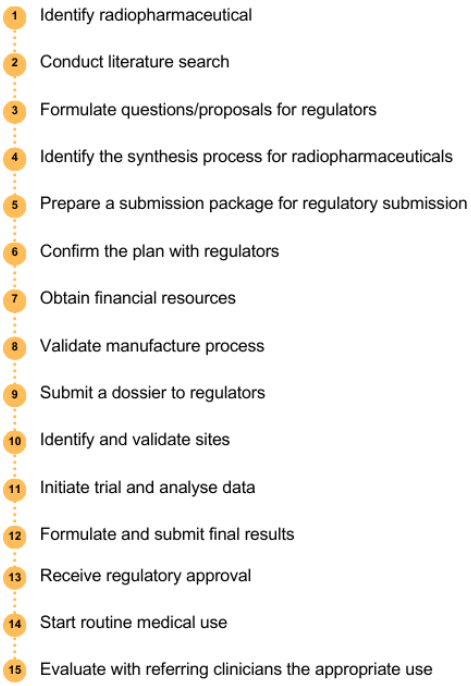


Figure 7. *Introducing Radiopharmaceuticals into Clinical Practice. Adapted from IAEA*

These references are valuable resources for simplifying and accelerating the integration of radiopharmaceuticals into clinical practice, leading to better diagnostic solutions and improved patient care. [85]

However, it is important to highlight that the current regulation only addresses diagnostic radiopharmaceuticals, which has led to the need for a revision to include therapeutic radiopharmaceuticals through collaboration with the EMA and the European Commission. This revision aims to facilitate rational and safe progress in the field of nuclear medicine. [71]

2.4. United States vs. European Union Perspectives

2.4.1. Radiopharmaceutical Clinical Trials - Europe

The regulatory framework in Europe and the changes introduced by the new regulation in clinical trials with radiopharmaceuticals have been previously discussed. However, not all European countries are EU members, and even within the EU, individual member states maintain considerable influence on legislation. This results in a heterogeneous regulatory landscape for radiopharmaceuticals. EU directives on pharmaceuticals must be adopted into each member state's national law, leading to potential interpretation differences and variations between nations. Additionally, some topics are primarily regulated by national governments rather than EU. [68]

As a result, the introduction and use of new radiopharmaceuticals in Europe currently follow two main pathways: one based on the EU–Clinical Trial legislation and specific guidelines and another based on specific national regulations. This discrepancy emphasizes the EU's limited authority in areas such as healthcare and pharmaceutical practices, which results in significant differences in the availability and application of radiopharmaceuticals in Europe. [68]

For instance, the recent changes in the regulation regarding GMP production have highlighted disparities. The preparation of radiopharmaceuticals is a vital task within the Nuclear Medicine community, particularly for clinical trials. Nuclear medicine departments actively participate in trials involving both diagnostic and therapeutic radiopharmaceuticals and there is an emerging and growing demand for new radiopharmaceuticals, especially those with short half-lives suitable for use with PET scanners. However, the regulation only covers diagnostic radiopharmaceuticals, while therapeutic radiopharmaceuticals are still subject to GMP production. [70]

A survey conducted by the EANM across seven European countries also concluded that there are still differences in the requirements for GMP. In France, GMP is not mandatory for radiopharmaceutical use in public hospitals, but the hospital's radiopharmacy must follow good preparation practice which is less strict. In Germany, GMP adherence depends on regional policies. Italy's GMP requirements differ based if the trial's commercial or not, while in Belgium, GMP is mandatory only for IMPs. Conversely, in Spain, the United Kingdom, and the Netherlands GMP is always mandatory. [71]

This survey demonstrated that the implementation of regulation is still incomplete, primarily due to national restrictions that contradict the provisions outlined in the EU regulation. [71]

2.4.2. Radiopharmaceutical Clinical Trials – United States

Developing radiopharmaceuticals, conducting clinical trials, translate them for clinical practice, while meeting regulatory standards are costly challenges in the United States, similar to the European Union. Diagnostic radiopharmaceuticals face even greater hurdles due to lower reimbursement rates compared to traditional therapeutic drugs. To address these issues, US regulatory agencies have collaborated closely with the radiopharmaceutical industry to facilitate the efficient introduction of new radiopharmaceuticals into clinical trials, while maintaining compliance with the existing regulatory framework and pharmaceutical development laws. [90]

Clinical Research in the United States falls under the authority of the Food and Drug Administration (FDA), which includes radiopharmaceuticals. The clinical trial application for radiopharmaceuticals to the FDA can occur through two mechanisms: an Investigational New Drug (IND) application or via the Radioactive Drugs Research Committee (RDRC). [68]The RDRC is an institutional committee approved by the FDA, responsible for reviewing and approving human research involving radioactive drugs or biological products (without an IND), particularly when the research is of a basic nature and not intended to guide clinical decisions. [90]

Conducting clinical trials with radiopharmaceuticals within the RDRC program presents an alternative to the conventional process of submitting an IND application. The RDRC program comprises a multidisciplinary committee within the institution tasked with ensuring compliance with federal regulations outlined in Title 21 of the Code of Federal Regulation (CFR) 361.1 Radioactive Drugs for Certain Research Uses. This committee acts as the regulatory authority responsible for reviewing and approving internal RDRC applications, which include the clinical protocol and details on radiopharmaceutical manufacturing control. [92][90]

Studies conducted under the RDRC program must adhere to specific criteria to qualify:

1. The research aims to advance scientific knowledge in basic science.
2. The research study is approved by an FDA-approved RDRC
3. The radioactive drug's pharmacologic dose is confirmed to have no clinically detectable pharmacological effect in humans.
4. The radiation dose administered is justified by the study's quality and the importance of the information sought, staying within specified limits (Food and Drug Administration)

The process of submitting an IND application involves several steps:

1. **Pre-Investigational New Drug (IND) Meeting:** Before submission of documentation, the FDA encourages applicants to schedule a pre-IND meeting to assist in preparing a development strategy. The request is usually in writing, listing the objectives for the meeting. [68]
2. **Investigational New Drug (IND) Application:** An IND is a request from a clinical study sponsor to obtain authorization from the FDA to administer an investigational drug or biological product to humans. [94]

These applications include information on pharmacology and toxicology testing from preclinical testing in animals. In the IND application, developers must include:

- Animal Pharmacology and Toxicology Studies
- Manufacturing information
- Clinical protocols and Investigator Information [95]

3. **FDA Review**: Once the IND is submitted, the FDA requires 30 calendar days to review and present preclinical, clinical, or CMC-related questions. At the end of this review, if the FDA's questions are adequately addressed, it will send a ''may proceed'' letter to the principal investigator or sponsor, who will then submit this letter to the institutional review board. [94]

4. **IND Approval:** FDA responds to IND applications in one of two ways: Approval to begin clinical trials or Clinical hold to delay or stop the investigation. A clinical hold is rare; instead, FDA often provides comments intended to improve the quality of a clinical trial. In most cases, if FDA is satisfied that the trial meets Federal standards, the applicant is allowed to proceed with the proposed study.[68,94]

5. **Post-Approval Monitoring:** To meet this goal, FDA has in place postmarketing programs that monitor marketed human medical products for unexpected adverse events. These programs alert the Agency to potential threats to the public health. Agency experts then identify the need for preventive actions, such as changes in product labeling information and, rarely, re-evaluation of an approval decision. [94]

In addition to the IND application, there are other categories, such as exploratory INDs(eIND) and expanded access INDs (eaIND). [90]

The exploratory IND application process was developed to streamline pharmaceutical discovery and drug candidate selection, which are costly and time-consuming processes. The advantages of this category include, for example, a reduction in the submission of preclinical data (such as toxicology tests in only one animal species instead of two), less stringent process validation, and fewer documentation requirements. [90,92]

On the other hand, eaIND allows the use of investigational drugs outside of clinical trials, aiming to treat patients facing serious or potentially life-threatening disease when there are no satisfactory alternative treatment options available. The rules and regulations related to expanded access aim to facilitate access to experimental drugs for patients who may benefit from therapies in the research phase. [96]

2.4.3. Comparative Analysis between United States and Europe

When analysing the requirements and submission procedures, it's evident that are some differences between the US and Europe. **Table 2** provides a comparison of the documents required for clinical trials.

***Table 2**. Documentation Required for Clinical Trials. Adapted from Schwarz*

PARAMETER	UNITED STATES	EUROPE
Submission Name	IND application	CTA
General	Form FDA 1571	EudraCT registration
	Table of contents; introductory statement	CTA application form for competent authority and ethics committee
Related to clinical trial conduct	General investigation plan	Protocol synopsis
	Clinical protocol	Clinical trial protocol
	Informed consent form	Informed consent form
	Case report forms, standard operating procedures, etc.	Case report forms, standard operating procedures, etc.
Related to radiopharmaceutical	Investigator's brochure	Investigator's brochure
Others	Dosimetry; letter of access to cross-referenced IND or master file (if applicable)	Additional information (facility and staff, financial issues [insurance, compensations, agreements])

At this stage, it is also important to analyse the number of clinical trials conducted in each region (**Chart 3**). Using the clinicaltrials.gov database, active radiopharmaceuticals clinical trials in January 2024 were searched for. In the United States, 58 ongoing clinical trials were identified, of which 37 were for diagnostic radiopharmaceuticals, and the remaining 21 were for diagnostic. While in Europe, there were 11 ongoing trials, with the majority being for therapeutic radiopharmaceuticals (8 trials).

It can be assumed that the low numbers in Europe are attributed to strict regulatory requirements, lack of funding for investigator-initiated studies, and lack of motivation among professionals, among other factors. Additionally, the process of submitting clinical trial applications in the United States has facilitated the pathway for radiopharmaceuticals, as there are different types of submission categories and the possibility of submitting to a specific committee for radiopharmaceuticals.

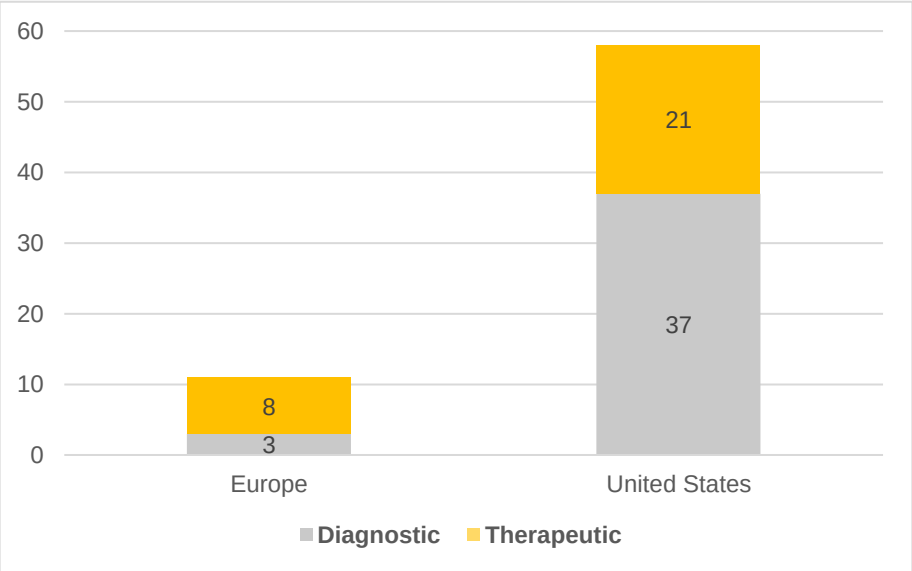


Chart 3. *Active Radiopharmaceutical Clinical Trials. Source: ClinicalTrials.gov*

There are similarities in the requirements between Europe and the United States, such as the obligation to follow GCP and include clinical trial protocols, informed consent forms, and an investigator brochure in the submission. The recognition of radiopharmaceuticals as a special category of medicines, along with the administration of microdoses, and the FDA's efforts to relax requirements for animal toxicity testing, are also notable. However, these similarities are not consistent, especially in Europe due to its layered hierarchy. [68]

Different regulatory requirements impede new radiopharmaceutical research, limiting patient access to these advancements. Additionally, the lower visibility of radiopharmaceuticals compared to other therapeutic drugs has led to a reduction in the availability of these products in many countries.

Regarding the recognition of radiopharmaceuticals in the New European regulation, there is still intense debate over whether national authorities will fully implement a reduction in GMP requirements. [68]

Radiopharmaceuticals represent a small market compared to the global therapeutic drug market, and the lack of specific attention from the ICH for these products reflects this lower visibility. IAEA has identified these issues as problematic and is seeking a global discussion to harmonize specific regulations for radiopharmaceuticals. [68]

Chapter III

Activity Report

3. Host Instituition

CRU^2C (Clinical Research Unit University of Coimbra) is a clinical research unit at the University of Coimbra, linked to the Institute of Nuclear Sciences Applied to Health (ICNAS), which provides support to sponsors and researchers in complying with GCP guidelines and national and international regulations. ICNAS, founded in 2009, is a multidisciplinary research unit at the University of Coimbra and a leading medical imaging facility. It focuses on fundamental and clinical research, collaborating with national and international partners in medical imaging and translational research. CIBIT is its research unit.

ICNAS is a pioneer in:

- Collecting and analysing data in molecular medicine;
- Development of new molecular markers;
- Advanced research into multimodal imaging techniques;
- Structural and functional medical imaging;
- Translational biomedical research.

It acts as an external imaging site for procedures performed during industry sponsored clinical trials, in the modalities of magnetic resonance imaging (MRI) and positron emission tomography (PET) in more than 30 clinical trials, especially in the fields of oncology, cardiology, and neurology. Therefore, CRU^2C works with both commercial and academic clinical studies.

It has three pillars: research, education, and integration with the National Health Service (SNS). Within the SNS, it plays an important role in imaging exams and the distribution of radiopharmaceuticals to the country's main hospitals.

ICNAS has a production unit with two cyclotrons and a radiopharmacy for synthesizing radiopharmaceuticals. ICNAS-PHARMA, a company affiliated with UC located within ICNAS, is responsible for operating the cyclotrons, focusing on the production, quality control, and availability of radionuclides and radiopharmaceuticals.

In general, the activities carried out at ICNAS can be grouped into three main aspects, where the functions performed by ICNAS and ICNAS-PHARMA complement each other:

Production of radionuclides and radiopharmaceuticals for clinical or research purposes under the responsibility of ICNAS-PHARMA;

Research at various levels (basic, non-clinical, and clinical), with CIBIT as its research unit, involving both ICNAS and ICNAS-PHARMA;

Provision of specialized healthcare services in the fields of biomedical imaging, with responsibility attributed to ICNAS.

ICNAS has a multidisciplinary team with expertise in fields such as medicine, engineering, mathematics, physics, computer science, and pharmaceuticals, among others, ensuring the proper execution of all activities related to production, research,

and service provision, and ensuring the achievement of established fundamental objectives.

CRU^{2}C offers not-for-profit rates expertise to support all stages of clinical research, complying with ethics and regulatory authorities, to successfully reach high-quality, efficient, and sustainable clinical research.

The services performed by CRU^{2}C include:

- Support on Funding Application
- Assistance in the preparation of essential trial-related documents such as the protocol, patient informed sheets and informed consents
- Budget estimation
- Regulatory Affairs
- Clinical Study Management & Monitoring
- Biostatistics and Data analysis

3.1. Curricular Internship Objectives

Since it is the final component of the Master's in Clinical Research Management, the primary aim of the internship was to consolidate and apply the knowledge acquired during the theory classes. More specifically, the objectives were:

- **Clinical Research Unit (CRU) experience:** Gain hands-on experience in a Clinical Research Unit, demonstrating comprehensive knowledge of the various components of clinical research.
- **Clinical Study Activities:** Engage in activities related to the organisation, planning, implementation, and monitoring of clinical studies.
- **Quality Processes:** Draft, review, and maintain quality processes, including creating and revising Standard Operating Procedures (SOPs).
- **Soft Skills Development:** Reinforce the transversal skills essential for a real work environment, such as proactivity, autonomy, communication, and problem-solving.
- **Self-Learning and Research:** Improve the ability for self-learning, research, and selecting relevant information through the assigned tasks.

A secondary objective of the internship was to develop a project with a differentiating theme of interest to ICNAS, in collaboration with the respective team, to be presented in the internship report.

Specific objectives

The main functions assigned throughout the internship included Clinical Trial Assistant (CTA) and Start-up Specialist activities. **Table 3** shows the tasks planned for the internship at CRU^{2}C.

***Table 3**. Plan of activities for the internship at CRU^{2}C*

Activity Plan
Preparation of major documents
Development and/or revision of protocols
Development of other major documents: protocol synopsis and informed consent
CEIC and INFARMED submission
Preparation of dossiers for approval by INFARMED
Preparation of dossiers for approval by CEIC
Preparation of dossiers to request approval from the Health Ethics Commissions
Monitoring Activities
Monitoring plan (preparation)
Initial visits
Monitoring visits
Visit reports
Study Coordination
Daily monitoring of research teams
Identify potential participants for the clinical studies taking place at the test site

Organisation of internal logistics related to the execution of ongoing clinical studies
Monitoring initiation visits
Meetings with Sponsors
Organising and keeping the ISF up to date
Preparing and submitting requests for authorisation to carry out new clinical studies to the Board of Directors/Ethics Committee of the trial site.
Monitoring recruitment

3.2. Context of the internship

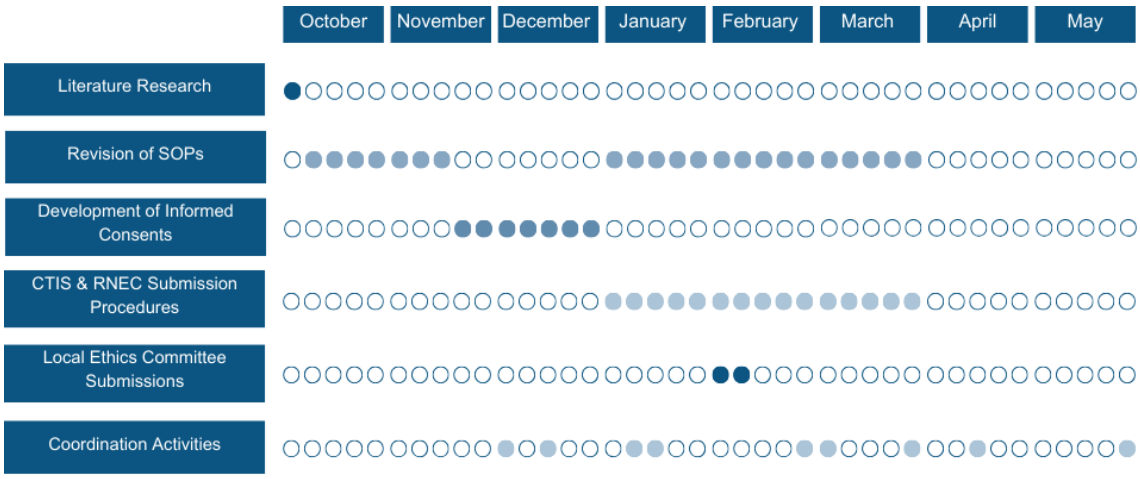
The internship is part of the Curricular Unit Dissertation/Project/Internship, of the 2nd cycle of studies of the master's degree in Clinical Research Management, which results from a collaboration between the University of Aveiro and NOVA Medical School.

The curricular internship took place between 9th October 2023 and 29th May 2024, under the scientific guidance of Professor Maria Teresa Herdeiro and the supervision of Doctor Ana Pina Rodrigues (Project Manager at CRU^{2}C) and tutorship of Doctor Sara Almeida (Clinical Trial Assistant at CRU^{2}C).

The first week of October was dedicated to literature research and the regulatory framework for clinical trials with medicines and interventional studies with medical devices.

Table 4 shows the timeline for the internship. In total, 774 hours of internship were completed.

Table 4. *Schedule of internship activities*



The internship activities can also be divided into therapeutic fields, as shown in **Table 5**.

Table 5. *Studies carried out during the internship*

Study	Therapeutic Field	Study Design	Phase	Sponsor	Activity Performed
ICNAS_1	Autism	Clinical Trial	Pivotal	Academic Investigator	Medical Writing, Set-up, Regulatory and Data Management Activities
ICNAS_2	Alzheimer	Observational	NA	Academic Investigator	Medical writing
ICNAS_3	Diabetes	Observational	NA	Academic Investigator	Coordination activities

3.3. Activities carried out during the internship

During the internship, tasks were developed in the scope of internal and external academia sponsored studies and in industry sponsored studies in which ICNAS acts as an external imaging site.

Tasks included developing and reviewing SOPs, attending a site initiation visit, developing informed consent for paediatric population, developing a CRF, completing the ethics committee submission form, and organising the external site dossier and they're explained in detail below.

3.3.1. Task 1 – Standard Operating Procedures Development/Revision

Quality in clinical research consists of compliance with requirements and the credibility and reliability of the data obtained. To guarantee this quality, sponsors generally implement quality management systems (QMS), which aim to ensure, control, maintain, and improve quality continuously and consistently. ISO 9000 defines QMS as a set of interactive elements established to direct and control an organisation concerning quality. [97]

In clinical research, the necessity of putting systems and procedures in place to ensure the quality of the clinical trial at every stage is also outlined in the thirteenth principle of the International Conference on Harmonization - Good Clinical Practice (ICH GCP). [98]

Implementing a QMS at a research organization is fundamental to effectively support clinical trial activities. This strategic decision increases the credibility and effectiveness of the organization. The main objective is to ensure the consistent application of the legislation, guidelines, and associated regulations covering clinical research. The main advantages include improving organisational performance and establishing a solid foundation for sustainable development.[99]

In addition, a well-designed QMS must be adapted to the specific size and nature of the organisation, recognising its unique characteristics and operational requirements.

Although some activities are related, quality assurance (QA) and quality control (QC) are two different concepts in quality management. While QC is a subset of QA activities, QA activities and responsibilities usually encompass almost the entire quality system in one way or another (**Figure 8**).[100]

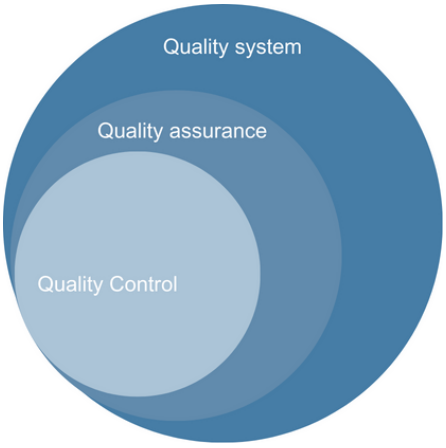


***Figure 8**. Quality System, Quality Assurance, and Quality Control Relationships. Adapted from ASQ*

ISO 9000 defines QC as a set of activities and techniques applied to ensure that all quality requirements are consistently met.[97]

Quality assurance can be defined as “part of quality management centred on ensuring that quality requirements are met”. In clinical research, this includes all systematic and planned actions implemented in the quality system to ensure that the study is carried out and that the results are produced, documented, and reported following the applicable GCP and regulatory requirements.[98,99] Quality assurance therefore focuses on preventing errors and ensuring that systems and procedures are in place to provide consistent and satisfactory results.[100]

Quality documents cover a variety of materials that support quality management and quality assurance within an organisation. These documents include company policies, quality management plans, Standard Operating Procedures (SOPs), work instructions, conventions, guidelines, forms, templates, records, labels and tags. The hierarchical structure and types of quality documents relevant to an organisation's quality systems are not universal. Each organisation must develop and organise its quality documents in a way that best supports its objectives.[98]

In this context, the first activities that were carried out during the internship were the preparation and revision of SOPs along with reports and templates to improve and complement the quality management system.

According to the ICH-GCP, SOPs are "detailed written instructions for achieving uniformity in the performance of a specific function". A SOP contains responsibilities for carrying out a procedure, the resources needed for the procedure, where and when it should be carried out, and how the person responsible will carry out the procedure.

SOPs are essential for standardising processes, minimising variations, and ensuring that products and services consistently meet quality requirements. They play a crucial role in the ability of sites to achieve the specific parameters outlined in the protocol while guaranteeing the reproducibility and consistency of information. SOPs serves as

an essential tool for achieving the goal of data robustness, providing a clear path for the precise execution of the procedures. [101]

To effectively control GCP compliance and prevent errors from occurring, SOPs must be well written. They must be clear, unambiguous, and written in simple language. A good SOP enables good process management, eliminates waste, improves speed, reduces costs and variation, and guarantees quality and precision. A poorly written SOP becomes a source of misinformation. [98]

Any modifications to the SOPs must be reapproved and they must be reviewed and updated as needed during their life cycle. [98]

Clinical trials involving medical imaging face a variety of challenges, especially concerning the logistics of the study and the team of technicians, the standardisation of the techniques used and data analysis, and regulatory compliance.

To deal with these challenges CRU2C has created many SOPs such as Positron Emission Tomography/Computed Tomography (PET/CT) Scan acquisition and Magnetic Resonance (MR) Scan acquisition.

In the case of radiopharmaceuticals, which require additional supervision due to their radioactive component, nuclear medicine departments develop SOPs to ensure compliance with all requirements. These SOPs address the use of experimental radioactive materials following the guidelines set out in the ICH (E6 4.6.3). [101]

Figure 9 shows the SOPs and associated documents developed during the internship.

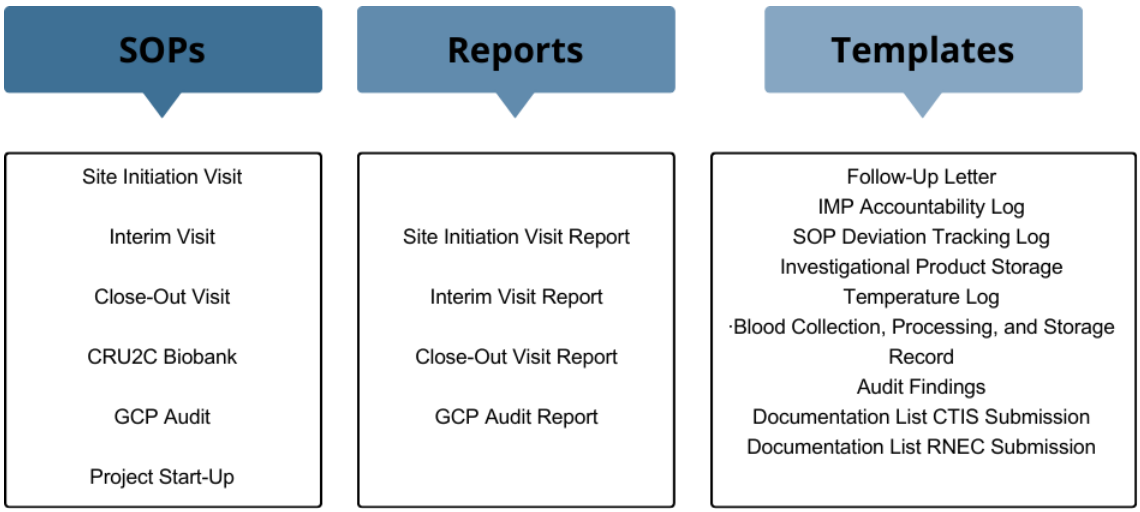


Figure 9. *Documentation developed during the internship*

The structure of the SOPs consisted of the following topics:

Purpose: Why it was written. It should expand on the title and be in line with the topics in the procedures section.

Scope: When the SOP should be used.

Abbreviations and definitions: Clarification of the meaning of the acronyms used in the SOP.

Responsibilities: Who it applies to. It includes all the roles listed in the responsibility column of the procedures section.

Procedures: Who should operationalise it. This section lists a logical sequence of step-by-step actions required to perform a task.

Annexes: They help to apply the SOP.

References: These include regulations, guidelines, laws, or documents needed to complete the task; they are prerequisites for being able to start carrying out the SOP steps.

Document history: Record of the main changes to the SOP.

Approval: Who wrote and approved the SOP.

The preparation of the SOP for site initiation visits and complementary documentation will be discussed in more detail.

SOP of Site Initiation Visit

According to the ICH-GCP guidelines, the monitor should visit the site at least once before the start of the study. The site initiation visit is essential to ensure that staff are qualified and competent to carry out the proposed tasks, that the necessary facilities and tools are available, that the rights and safety of participants are protected, and that data are collected accurately to ensure their robustness. [102]

The initiation visit is an integral part of the quality control of the clinical trials and is designed to ensure the quality of the trial according to the sponsor's requirements and to ensure that all necessary documents are in place to facilitate appropriate conduct and ongoing documentation of the trial.

The SOP for the site initiation visit was the first to be prepared. The following documents were also developed:

- Site Initiation Visit Checklist/Report
- Follow-up Letter
- Investigational Product Accountability
- SOP Deviation Tracking Log
- Investigational Product Storage
- Temperature Log

The procedures for this SOP were divided into three sections: preparation, conduct, and post-visit.

When **preparing for the visit**, the monitor must carry out several essential activities to ensure that everything is in order before the meeting with the site team. The

monitor's main responsibilities during this preparation phase include confirming regulatory and ethical approvals, reviewing the protocol and essential documents, coordinating with the site team, planning logistics, checking the functioning of platforms, and preparing documentation to be used during the visit.

The monitor's main activities and responsibilities **during the visit** include training the team on the protocol and specific activities of the trial, discussing and checking the items covered in the SIV report, reviewing essential documents, checking facilities and equipment, managing IMPs if applicable, reviewing safety procedures, delegating tasks, among others.

After the visit, the monitor still must ensure that the site is fully prepared to take part in the study and to maintain compliance throughout the trial. This is achieved by preparing the visit report, identifying any problems, and following them up, and, if necessary, providing additional training.

The site initiation visit activities can be summarised in **Figure 10**.

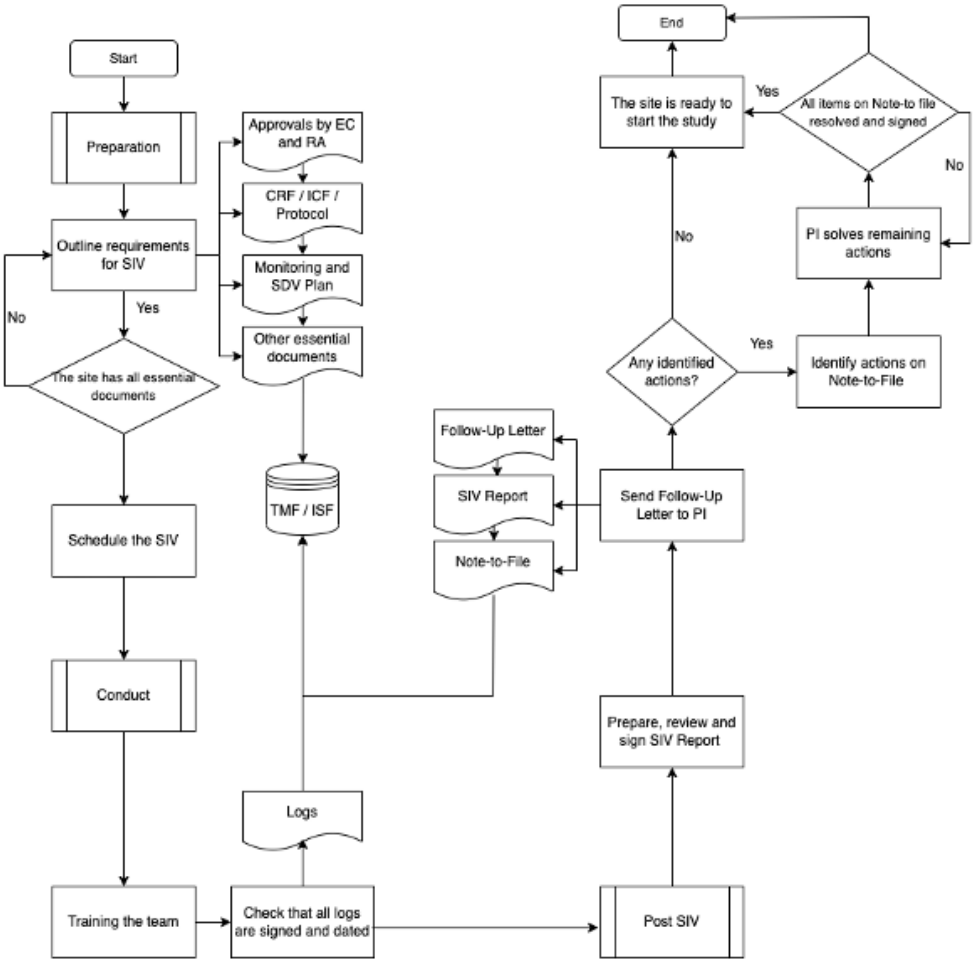


Figure 10. *Flowchart of the SIV activities*

The Site Initiation Visit Report was divided into several parts, including:

- Aspects of the team
- Regulatory aspects
- Protocol/Investigator's Brochure (IB) Summary of Product Characteristics (SmPC)/Instruction for Use (IFU)
- Participants recruitment
- Participants Informed Consent/Enrolment
- CRF/SDV
- Essential documents, ISF/TMF
- Protocol/ GCP deviations
- Safety reporting requirements and responsibilities
- Aspects about intervention (if applicable)
- Monitoring
- Laboratory aspects (if applicable)
- Facilities/equipment/study material
- Contracts, agreements, and insurance (if applicable)

3.3.2. Task 2 - Site Initiation Visit – as an external imaging site

During the internship, there were no monitoring visits at ICNAS, but there was the opportunity to attend an initiation visit by a Clinical Research Organisation (CRO), in a trial in which ICNAS was the external imaging site.

The visit was carried out by a CRO monitor, who introduced the team and discussed the objectives of the visit. A review of the protocol was carried out along with the inclusion and exclusion criteria. A more detailed review of the imaging procedures was given, specifically for PET/CT and instructions were provided about the image submission software. A discussion was held to answer any questions about the study.

Lastly, it was ensured that everyone present signed the delegation log and three technicians were trained on the image submission software.

3.3.3. Task 3 - CTIS platform training

As part of the preparation for the submission of clinical trials with radiopharmaceuticals, different activities were carried out to ensure compliance with regulatory requirements and optimise the submission process in the CTIS system. The activities included training in the use of the CTIS platform through webinars, workshops, and support materials from the EMA, revision of the SOP "Submission and Management of Clinical Trial Applications in Portugal and EEA - CTIS", and the creation of a list of documentation required for clinical trial submission.

These measures have ensured that the team is well prepared, processes are standardised and compliant, and all submissions are complete and accurate, facilitating the success of clinical trials and regulatory compliance.

CTIS is the single-entry point for submitting clinical trial information in the European Union. All communications, including the final decision from the authorities, are received via CTIS. With CTIS, sponsors can apply for clinical trial authorization in multiple EU/EEA countries with a single application.

Three types of applications can be submitted in CTIS for a trial:

- **Initial CTA:** The first submission for authorization to conduct a clinical trial. It includes comprehensive information about the clinical trial for the evaluation by the Member State Concerned (MSC). [103]
- **Additional MSC CTA:** This application is submitted when a sponsor wants to extend an already authorised clinical trial to additional Member States. [103]
- **Substantial modification CTA:** When the sponsor needs to make significant changes to an ongoing clinical trial. These modifications could impact the safety or rights of the trial participants or the reliability and robustness of the data generated. [103]

Initial CTA

To complete an Initial Clinical Trial Application (CTA) on CTIS, the sponsor will have to populate the following four main sections – Form, MSC, Part I, and Part II (**Figure 11**). [104]

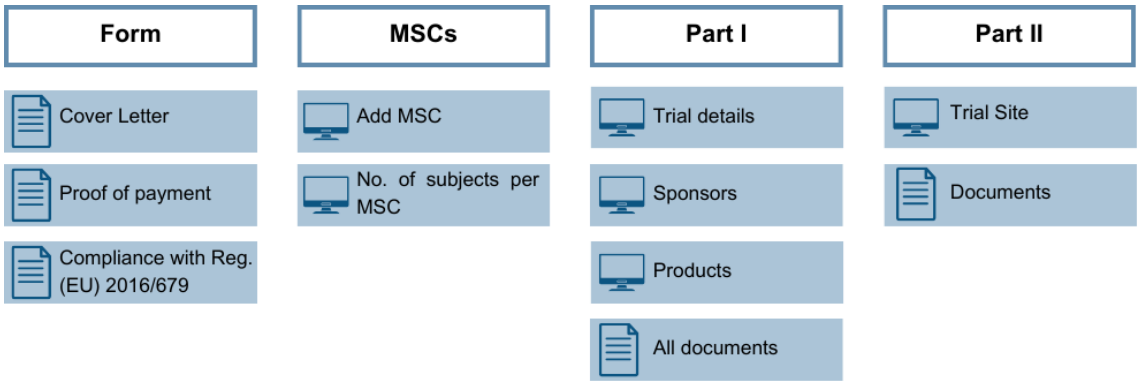


Figure 11. *Main Sections of Initial CTA. Adapted from EMA* [104]

"Form" displays information on the application form details including cover letter, proof of payment of the fee, and the compliance with regulation (EU) 2016/679[104,105]

In the **"MSC"** section, users must specify the MSCs for the trial they intend to conduct and the number of participants to be recruited in each of them. In the case of multinational CTA, users need to select a proposed MSC. If applicable, they should also present the countries outside the EEA where the trial will be conducted. [104,105]

“Part I” contains trial, sponsor, and product-specific information such as study protocol, trial design, eligibility criteria, therapeutic area, Investigator Brochure, the Investigational product dossier, and countries outside the EEA included in the trial. [104,105]

"Part II" contains documentation related to aspects that concern each of the MSCs where the trials are to be carried out, e.g., the Informed Consent Form and, subject recruitment arrangements, trial sites, etc. [104,105]

Additional MSCs application

An additional MSC CTA is an application submitted to extend a clinical trial that has already been authorized in one or more EU Member States to additional Member States. Generally, an additional MSC application can be submitted when there are no other applications for the same clinical trial currently under evaluation. However, it is possible to submit and add MSC CTA if there is an ongoing assessment for a substantial modification of part II in other Member States or if there are already other additional MSC applications under evaluation.[105]

Substantial Modification CTA

The concept of Substantial Modification (SM) in clinical trials refers to any change made to a clinical trial after a decision has been made on the initial application. A substantial modification includes changes that are likely to have a substantial impact on either the safety or rights of the subjects or the reliability and robustness of the data generated.[106]

If a change does not meet these criteria but is still relevant for supervision purposes, it may be classified as a non-substantial Modification.

Under Chapter III of the Clinical Trial Regulation, there are different types of SMs based on the parts of the application affected: SM of part I only, SM of part II only, and SM of parts I and II. Additionally, SMs can further be categorized based on the number of trials affected: [105]

• Single-trial SM: Applied when changes concern only one specific clinical trial.

• Multi-trial SM: Applied when changes affect multiple trials conducted by the same sponsor using the same investigational medicinal product. This requires specifying the EU Clinical Trial number for each trial affected. [105]

SMs can be submitted by the sponsor once a decision has been issued or tacitly approved for the previous application. Generally, an SM cannot be evaluated if there is another application under assessment (such as an initial application or another SM request). However, there are exceptions:

- Parallel assessment of Part II SMs: It’s possible to submit an SM application for Part II in one MSC while another Part II SM application is under assessment in a different MSC.
- Additional MSC CTA: An additional MSC application can be submitted while an SM application for Part II is being assessed in another MSC. [105]

Non-Substantial Modifications

A Non-SM refers to a change made to any aspect of a clinical trial that is not expected to have a substantial impact on the safety or rights of the trial subjects, nor on the reliability and robustness of the data generated in the trial. Despite not meeting these criteria, the change is still relevant for the supervision of the trial. [105]

Unlike Substantial Modifications (SM), which require formal evaluation and approval by the Member State Competent Authority (MSC), a Non-SM does not undergo this evaluation process. [105]

A Non-SM can be submitted once a decision or tacit approval has been received on a previously submitted application. It's important to note that a Non-SM cannot be processed while other applications (such as initial applications or SM requests) are under evaluation.

These changes can also be submitted in response to Requests for Information (RFIs) if required by the regulatory authorities. [105]

3.3.4. Task 4 - Informed Consent for Vulnerable Populations

During the internship, different informed consents were prepared, and adapted for different age groups, as part of a clinical study with intervention in an autistic pediatric population.

Autism Spectrum Disorder (ASD) is a neurological and developmental condition that impacts how individuals interact, communicate, learn, and behave. Symptoms usually appear within the first two years of life. The term "spectrum" indicates the wide range of symptoms and severity experienced by individuals with ASD.[107]

The abilities and needs of people with autism can change over time. Some individuals with autism can live independently, while others may have severe disabilities that require life-long care and support.[108]

They may find it challenging to communicate and interact with others, struggle to understand others' thoughts and feelings, experience sensory sensitivities, such as discomfort with bright lights or loud noises, feel anxious or upset in unfamiliar situations and social events., take longer to process information, engage in repetitive behaviors or thoughts, etc. [107]

Evidence-based psychosocial interventions can improve communication and social skills, which enhances the well-being of people with autism and their caregivers. Effective interventions and treatments can significantly improve symptoms and daily functioning, helping them to live more fulfilling lives. [108]

Medical Devices - Brief Framework

A class IIa medical device was used for this study.

Regulation (EU) 2017/745, also known as the Medical Devices Regulation, became effective in May 2017 and applicable from May 20221. This regulation replaced the previous directives, 93/42/EEC and 90/385/EEC, establishing a new regulatory framework to guarantee the safety and performance of medical devices in the European Union. [109]

The regulation defines a medical device as any instrument, apparatus, equipment, software, material, or other article intended to be used, alone or in combination, for medical purposes in human beings, for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, among others. Medical devices are categorised into four risk classes based on the duration of contact with the body, invasiveness, the anatomy affected, and the potential risks arising from technical design and manufacture:

- Class I: Low risk.
- Class IIa: Medium risk.
- Class IIb: Medium/High risk.
- Class III: High risk.

The MDR introduces stricter requirements for conformity assessment, post-market surveillance, and transparency of information on medical devices. It also strengthens the criteria for the clinical investigation of medical devices, requiring robust clinical data to demonstrate the safety and efficacy of devices before they are placed on the market. [109]

In clinical research, the regulation establishes detailed rules for conducting clinical trials with medical devices, ensuring that they are conducted ethically and scientifically. This includes requirements for obtaining informed consent, protecting participants, monitoring trials, and reporting results. [109]

Preparation of informed consents

To participate in clinical trials, participants must give their written informed consent, which guarantees that are fully aware of what they are agreeing to and exercising their free will to participate. [110] Informed consent is defined in the Clinical Research Law as “the express decision to participate in a clinical study, taken freely by a person who can do so or, failing that, by his or her legal representative, after having been duly informed of the nature, scope, consequences, and risks of the study, as well as the right to withdraw from it at any time, without any consequences...”[111]

Consent must provide a clear and transparent description of the purpose of the study, identify the researcher responsible for processing the data, and their contact details, and mention the scope of the study. [111]

In addition, the consent must include the possible risks, rules, guarantees, and associated rights, options to refuse or withdraw consent at any time, guarantee of data security and confidentiality, and all data processing activities carried out. [111]

The personal data requested must be adequate and limited to the research objectives. The purpose of the data processing must be made explicit in the consent and there must also be a question asking for the participant's authorisation to process and store the data for a well-defined period.

Patients are by themselves considered vulnerable, and within this group, some present greater vulnerability. This includes those at the extremes of age, such as children and the elderly, coma patients, those with mental disabilities or psychiatric disorders, those affected by drug-induced cognitive disorders, dementia, refugees, or populations at war, among others. [112]

Many of these patients lack the cognitive capacity to understand and decide about their participation in clinical trials/studies. Therefore, obtaining informed consent from these patients involves complex issues, as it requires not only the patient's understanding but also the ability to provide adequate information and obtain genuine consent. [112]

The patient needs to understand that, unlike what happens in clinical practice, where medical care is intended for the patient's benefit, clinical research is primarily aimed at the benefit of others and may occasionally result in direct benefits for the participants themselves. [112]

Informed consent is intended for patients who have reached the age of 16, except for individuals with mental disabilities. However, when it comes to pre-school children, primary school children, and adolescents, the decision-making process is more complex and in addition to the parent's and doctor's participation, it also involves the child's assent. [112]

Assent is the child's express agreement to the proposed medical treatment, recognising that they may not have full decision-making capacity or authority. [112]

Given the vulnerability of these participants, the researcher must take extra ethical care when obtaining consent. The minor's manifestation of desire must be recognised, and in advanced stages of maturity, even respected. [110]

When the participant's will goes against their parent's or representative's, the researcher must evaluate the child's/adolescent's ability to exercise autonomy, since parental consent will not be enough to validate participation. [110]

The Ethics Committee for Clinical Research (CEIC) has recommended a model for obtaining informed consent in pediatrics, shown in **Figure 12**.

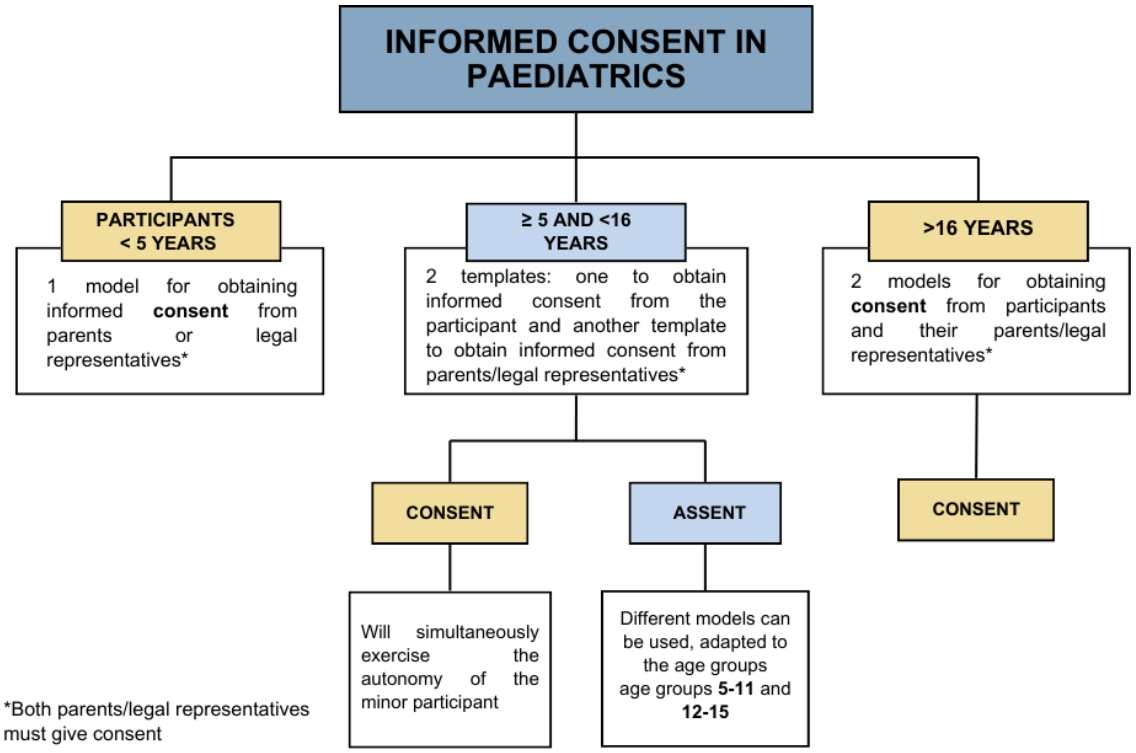


***Figure 12**. Diagram of informed consent/assent models*

The CEIC recommendations were considered when drawing up the informed consents and assents, resulting in the set of documents:

- Informed assent for children from 7-11 years old;
- Informed assent for children from 12-15 years old;
- Informed consent for teenagers aged 16-17years old;
- Informed consent for parents.

When performing this task, one of the biggest challenges encountered was determining the appropriate language and type of information to include in the documents. The assents must be easily readable and quickly understood by the child. [113] It was therefore necessary to adapt the language and include illustrations for each age group to make it easier for children to understand.

It is important to provide the child with as much information as they can understand, considering the nature of the research and the child's level of maturity. [113] This was

particularly important when dealing with younger children, where certain information may not be appropriate or understood.

Figure 13 illustrates one of these examples. The withdrawal of consent/assent section provides a more detailed explanation of the procedure for children over 16, while simplified language is used for children between 7 and 11.

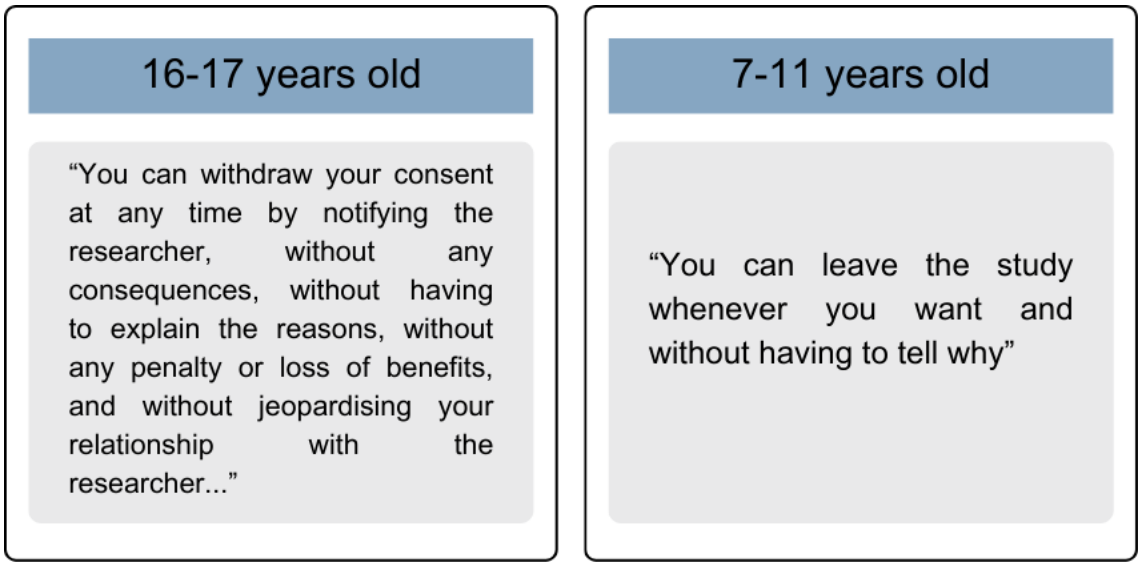


Figure 13. *Example of language used according to the age of te children*

3.3.5. Task 5 - Developing a CRF

A Case Report Form (CRF) is a crucial document in clinical research, serving as a document to capture essential data about each participant in a trial. As outlined by the ICH-GCP, CRF can exist in physical, digital, or even optical formats. [14] Their primary purpose is to document every detail required by the trial protocol to be reported to the sponsor for every trial subject. [114] Its development isn't just a procedural step, but also a quality step to ensure that the information required by the protocol, regulatory standards, safety requirements, and study-specific hypotheses is recorded, thereby influencing the success of the trial. [114] By providing a structured framework, CRFs streamline the collection, processing, analysis, and communication of data efficiently and completely. [115]

The creation of the CRF is intended to ensure the accuracy and consistency of the data, so it must be arranged to analyze the data more straightforwardly. A multidisciplinary team works on the CRF so that all users—researcher, center coordinator, study monitor, data entry personnel, medical coder, and statistician—must have their needs addressed.

Ideally, the CRF should be created as soon as the protocol is complete since it will determine the type of data that should be collected, including the measures defined in

the protocol. All data that will not be analysed in the protocol should not be included in the CRF. In addition, the CRF should be carefully structured to allow for easy and independent completion, to collect high-quality data. [114,115] If the data recorded in the individual CRF are inaccurate it can significantly impact the reliability and validity of the overall trial results. [116]

To ensure the efficacy and integrity of the data in clinical trials, the questions in the CRFs must be formulated clearly and concisely, avoiding duplication. [115]

In addition, a comprehensive interdisciplinary review of each CRF is essential, involving all relevant team members responsible for conducting, analysing, and reporting the clinical trial. [115]

The collection of basic information, such as the date of visit and general health condition measures, is common at all stages of a clinical trial. However, the endpoints and additional measures may vary according to the pathology being studied. [116]

The information is sent to the sponsor's database after it has been gathered. After reviewing the data for errors, the sponsor can ask the site to provide more information. Throughout the data-collecting procedure, ongoing reviews are conducted to guarantee the clinical study's continuity and safety. [116]

During the internship, a CRF was developed for a study related to Alzheimer's disease. The process involved several key steps to ensure that the CRF was comprehensive and accurate for collecting the necessary data. Firstly, comprehensive research into the condition was carried out to understand the clinical aspects of the disease, common symptoms, and diagnostic criteria. In addition to clinical information, the CRF also included data on the participants such as age, gender, ethnicity, and level of education, which is important for understanding the sample demographics and carrying out appropriate statistical analyses.

Specific information needed for the study's hypotheses was identified for collection. For confidentiality reasons, only the information related to the pathology will be addressed in the present report.

Alzheimer's disease (AD) is the most prevalent form of dementia, characterized by the progressive degeneration of brain cells. It is primarily identified by the presence of neuritic plaque and neurofibrillary tangles, resulting from the accumulation of amyloid-beta peptide (Aβ) in the most affected region of the brain, the medial temporal lobe, and neocortical structures, and hyperphosphorylated tau (p-tau), a microtubule assembly protein that accumulates intracellularly as neurofibrillary tangles. [117,118]

Thanks to advances in research, it is now possible to detect biomarkers associated with dementia, allowing for more accurate and earlier diagnosis. [119]

In the case of patients with suspected Alzheimer's disease, it is common to carry out a neurological examination, brain magnetic resonance imaging (MRI), laboratory tests,

such as vitamin B12, and other tests, in addition to the patient's medical and family history. [117]

Figure 14 shows data highlighting these criteria and diagnostic methods, which were subsequently used in the CRF.

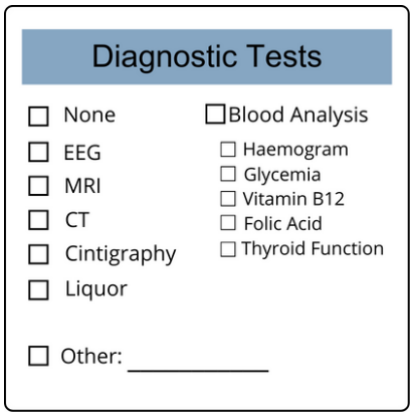


Figure 14. *Diagnostic tests mentioned in the CRF*

Based on the CRF, the monitor conducts source data verification (SDV) and checks if all the required data of the participant is correctly entered into the CRF and that these entries are consistent with the source documents, such as medical records and lab results. This process ensures that the data collected is accurate, complete, and consistent with the original information, ensuring the integrity of the study data and compliance with GCP.

3.3.6. Task 6 - Ethics committee submission form

The competent ethics committee is the body responsible for giving favourable opinions on clinical studies. Depending on the type of clinical study, this responsibility can be delegated to different ethics committees. According to the Clinical Research Law, in clinical trials and studies with medical devices, the competent ethics committee is the CEIC, unless it designates an ethics committee for this purpose. For all other clinical studies, the competent ethics committee is the ethics committee operating at the clinical study site involved or, if the clinical study site involved does not have an ethics committee, the CEIC or the committee appointed by them.

In my internship, I had the opportunity to participate in submissions to the local ethics committee of the Faculty of Medicine of the University of Coimbra (FMUC). There are different templates for the submission form, but the main information required is the same. This includes:

- Identification of the research team

- Identification of the project

- Scientific justification for the research

- Participants involved in the research: inclusion/exclusion criteria and how the study and control groups are recruited

- Other information about the project: whether complementary examinations will be carried out, whether questionnaires will be involved, other procedures

- Brief description of the research plan and methodology

- Risk/benefit assessment

- Protection of participant data

- Conflict of interest

- Consent

- Regarding the study: expected start and end date, reimbursements, insurance.

3.3.7. Task 7 - Study Coordination

Although the Principal Investigator (PI) is ultimately responsible for designing, carrying out, and managing the studies at the site, study coordinators play an important role in supporting, facilitating, and coordinating the day-to-day activities of the study. [120] They monitor the visits progress and help to maintain detailed records while adhering to strict regulatory guidelines and GCP standards to ensure the integrity and validity of the study results. [121]

From the beginning of December until the end of the internship, study coordination activities were performed in a study in which ICNAS acted as an external imaging site. The study included two imaging procedures, PET/CT and MRI for elderly diabetic patients.

Pathology addressed

Diabetes is a chronic metabolic disease that occurs when the pancreas doesn't produce enough insulin, or the body can't effectively use the insulin it produces. This results in high levels of glucose in the blood, and over time can lead to serious damage, particularly to the nerves and blood vessels.[122,123]

There are two main types of diabetes:

Type 1 diabetes: Chronic condition where the body's immune system mistakenly attacks and destroys the cells that produce insulin in the pancreas. [123,124]

Type 2 diabetes: The most common form of diabetes, occurs when the body doesn't produce enough insulin, or the cells don't react correctly to insulin. Unlike type 1, type diabetes is often associated with lifestyle factors such as being overweight, lack of physical activity, poor diet, and genetics. Management of type 2 diabetes includes lifestyle changes, oral medications, and sometimes insulin therapy. [123,124]

Around 422 million people worldwide have diabetes. In Portugal, more than 10 percent of the population is affected, with around 200 new patients diagnosed daily. [122,125,126]

3.3.8. Task 8 - External site dossier

One of the activities carried out during the internship was the preparation of external site dossiers. The Investigator Site File (ISF) is kept by the PI at the site where the trial is conducted and is used to record all activities and documents relevant to the conduct of the trial at that site. In contrast, the external imaging site dossier is specific to the sites that provide medical imaging services for the trial, but which are not the main site where the study is conducted.

The aim of the external imaging site dossier in a clinical study is to compile all the relevant information necessary for the proper conduct of the study, ensuring that the site team has all the information necessary to carry out the specific imaging tasks required by the protocol, complying with the GCP and applicable regulations, being an important instrument for the quality assessment of the trial.

It is therefore important that SOPs and image acquisition manuals are available to ensure that all external imaging sites perform consistently in acquiring, processing, and analysing images. Additionally, there are manuals for using the image submission software since these vary according to the sponsor.

The dossiers usually contain the following documents:

<u>Study procedure-related documents</u>

-Synopsis

-Protocol

-Image acquisition manual

-Image submission manual

-SOPs

-Other Relevant documents

<u>Logs</u>

- CVs of Staff included in the delegation log

-Training certificates (ICH-GCP, etc...)

-Site Signature Delegation log

-Site Training Log

<u>Administrative and financial related documents</u>

-Contracts

-Payment method

-Insurance

If there are new versions of these documents, it is important to revise the dossier to include the latest versions. In addition, older versions of the documents should be marked as out of date.

This consistency across external imaging sites is vital to maintaining the quality and integrity of the imaging data collected for the trial.

3.3.9. Courses taken during the internship

During my internship, I was encouraged to take part in different training programs and webinars to increase my knowledge and skills in the field of clinical research.

I participated in some AICIB training sessions, which aim to strengthen capacities and improve the performance and competitiveness of clinical research sites.

The topics were:

- **“Clinical Research Coordination Activities”**

- “**Management of clinical trial contracts”**

On 9 February 2024, the EMA held a webinar on **“Transitioning trials to the CTR (CTIS) for non-commercial sponsors”** which aimed to support non-commercial sponsors of clinical trials in transitioning their clinical trials to EU Regulation 536/2014.

In the medical devices sector, I participated in training sessions entitled **"Clinical Investigation and Device Performance Studies - From Theory to Practice"** which included 7 webinars that increased my knowledge of the European regulations on medical devices (EU 2017/745) and *in vitro* diagnostic medical devices (EU 2017/746).

In the final phase of the internship, I attended the **3rd National Meeting of Clinical Research and Biomedical Innovation**, a forum for sharing, reflection, and discussion on the most pressing issues in Clinical Research and Biomedical Innovation in Portugal.

3.4. Deviations from the activity plan

Deviations from the activity plan include activities that were initially proposed but were not performed, as well as those that were performed although they were not included in the initial plan.

For reasons beyond the control of the host institution, it was not possible to submit a clinical intervention study to the competent authorities during the internship, which is considered the most significant deviation.

Table 6 shows the activities planned and performed.

Table 6. *Activities performed in internship*

Activity Plan	
Preparation of major documents	**Performed**
Development and/or revision of protocols	✗
Development of other major documents: protocol synopsis and informed consent	✓
CEIC and INFARMED submission	**Performed**
Preparation of dossiers for approval by INFARMED	✗
Preparation of dossiers for approval by CEIC	✗
Preparation of dossiers to request approval from the Health Ethics Commissions	✓
Monitoring Activities	**Performed**
Monitoring plan (preparation)	✓
Initiation visits	✗
Monitoring visits	✗
Visit reports	✓
Study Coordination	**Performed**
Daily monitoring of research teams	✓
Identify potential participants for the clinical studies taking place at the test site	✗
Organisation of internal logistics related to the execution of ongoing clinical studies	✓
Monitoring initiation visits	✓
Meetings with Sponsors	✗
Organising and keeping the ISF up to date	✓
Preparing and submitting requests for authorisation to carry out new clinical studies to the Board of Directors/Ethics Committee of the trial site.	✓
Monitoring recruitment	✗

4. Discussion

Through the development of the 'Specifics of clinical trials with radiopharmaceuticals' project, many challenges were identified that require critical analysis, and the identification of possible solutions.

EMA has developed an extensive work to categorise risks and provide specific guidelines on dosimetry and non-clinical requirements for radiopharmaceuticals. These guidelines are fundamental for minimising the number of animal studies and adapting regulations to the unique characteristics of radiopharmaceuticals. However, implementing these guidelines presents challenges, particularly concerning harmonisation between different European countries and the complexity of GMP requirements for therapeutic radiopharmaceuticals.

The report compared regulatory requirements in Europe and the United States, which revealed some disparities. In the United States, the existence of specific submission categories and the possibility of submitting to specialised committees facilitate the process of clinical trials with radiopharmaceuticals. In contrast, Europe faces a more complex scenario, with strict regulations and a more bureaucratic submission process, which can discourage researchers and delay the development of new radiopharmaceuticals.

In Europe, another difficulty is the lack of funding, especially for investigator-initiated studies. Although the EU has established resources to support these trials, the practical application of these resources often encounters bureaucratic obstacles and a lack of motivation of the professionals.

Quality assurance and effectiveness regarding costs and time are critical factors in developing new radiopharmaceuticals. Using existing data on biodistribution, dosimetry, and safety profiles can speed up the introduction of new radiopharmaceuticals into clinical practice, saving time and resources.

Given the challenges, some of the possible solutions would be: harmonisation of regulations between different European countries, an increase in the financial resources available for investigator-initiated studies, which could motivate investigators to develop radiopharmaceuticals, and the use of already established data in clinical studies which could reduce the need to replicate studies.

Final considerations of the internship

The internship at CRU^{2}C offered valuable experience in the field of clinical research management. This discussion will cover the main aspects of the internship, including positive aspects, challenges, and skills acquired.

Several positive aspects of the internship can be recognised, being, the main one, the acknowledgment of the particularities of working in a CRU. A Clinical Research Unit (CRU) usually carries out the same level of work as industry. However, CRUs often operate with fewer resources, which means they have less funding, fewer staff and limited access to advanced technologies compared to industry stakeholders. Despite these limitations, CRUs deal with a wider range of research questions. They can

investigate various health conditions and use many research methodologies. This diversity is due to CRUs often being associated with academic or public health institutions, with the aim of exploring a broad spectrum of scientific questions, rather than focusing strictly on product development or specific therapeutic areas, which is common in industry.

In addition, many studies supported by CRU^{2}C involve medical devices, a topic not extensively covered during the master's theoretical classes. This made it possible to acquire practical knowledge about regulation, safety and efficacy assessment, and the specific procedures associated with testing medical devices.

A significant limitation of the internship was the lack of study submissions to CEIC and INFARMED. However, despite the absence of practical experience, during the internship, we have prepared the lists of documentation required for submitting the CTIS and completed an extensive CTIS training course.

One of the most challenging activities was adapting informed consent for children. There was a need to adjust the technical language to a more simplified one while maintaining the accuracy of the information. Furthermore, there were additional ethical considerations to ensure that children and parents/legal representatives understood the risks and benefits of the study. It was also necessary to use auxiliary materials, such as illustrations and schemes, to facilitate understanding.

My internship at CRU^{2}C enabled me to develop a wide range of skills. I developed project management, Clinical Trial Assistant, and Start-Up Specialist skills, communication skills, experience working in a multidisciplinary environment, and improved my critical thinking.

4.1. SWOT analysis

In line with the activities carried out during the internship, a SWOT analysis was carried out to recognise the strengths and critical points of the internship in order to improve the structure and organisation. This analysis is fundamental to gaining an in-depth understanding of the impact and effectiveness of the internship, highlighting the strengths that can be enhanced, the weaknesses that need to be addressed, the opportunities that can be exploited to maximise learning and innovation, and the threats that can impact the viability and sustainability of the projects.

Understanding these aspects makes it possible to promote practical and effective strategies to enhance the trainees' experience and improve the management of clinical research projects.

Strengths (internal factors):

- The internship provided me with significant hands-on exposure to research and development practices in the academic context.
- Possibility of working with renowned academics and researchers who are at the forefront of new discoveries and innovations.

- Internship at a respected institution in the field of nuclear sciences applied to health.
- Involvement from the initial planning to the execution of studies, thus being able to support all phases of clinical research.

Weaknesses (internal factors):

- Deviations from the activity plan.
- Public funding for investigator-initiated studies is very unpredictable compared to industry studies, which results in project delays.
- Potential delays in projects due to waiting for adequate funding, which can impact the continuity of studies.

Opportunities (external factors):

- Develop skills valued in the labour market.
- Participate in innovative research projects that can have a significant impact on health and science.
- Opportunity to explore areas less addressed by industry.

Threats (external factors):

- The lack of stable funding can jeopardise the viability and continuity of projects.
- Little attraction to the academic context, which leads to a lack of specialised human resources.

5. Conclusion

The challenges identified in the “Specifics of clinical trials with radiopharmaceuticals” project highlight the need for critical analysis and viable solutions. The EMA and IAEA have played a crucial role in developing guidelines for clinical trials with radiopharmaceuticals. However, the implementation of these guidelines faces significant obstacles. Comparison with the United States reveals a more facilitated and less bureaucratic approach, which could encourage more investigators and speed up the development of new radiopharmaceuticals. Solutions such as harmonising regulations, increasing funding for investigator-initiated studies, and using existing data can mitigate these challenges and promote significant advances in radiopharmaceutical research and development. The comparison with the United States and the solutions presented can provide a model and contribute to the advancement of radiopharmaceutical research in Europe.

The internship at CRU^{2}C provided an enriching experience, enabling the development of essential skills and serving as a complement to the master's theoretical classes. Positive aspects such as contact with clinical research management in academia and involvement and greater knowledge regarding medical device studies were notable. Overall, the internship at CRU^{2}C expanded my skills, mainly due to the multidisciplinary nature of the activities carried out and prepared me for future challenges in clinical research management.

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