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SARA FANECA DE OLIVEIRA

RELATÓRIO DE ESTÁGIO CURRICULAR NA NOVARTIS FARMA PORTUGAL

CURRICULAR TRAINING REPORT AT NOVARTIS PHARMA PORTUGAL

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Relatório de Estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Gestão de Investigação Clínica, realizada sob a orientação científica da Prof. Doutora Nélia Gouveia, Professora Auxiliar Convidada do Departamento de Ciências Médicas da Universidade de Aveiro e Investigadora Auxiliar da NOVA Medical School/Faculdade de Ciências Médicas da Universidade Nova de LIsboa

“Põe tudo o que és na mais pequena coisa que faças”

Fernando Pessoa

o júri

Presidente	Professora Doutora Maria Teresa Ferreira Herdeiro professora auxiliar da Universidade de Aveiro
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agradecimentos

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À minha família e amigos pelo apoio incansável e por contribuirem todos os dias para a minha construção pessoal.

palavras-chave

Estágio Curricular, Investigação Clínica, Indústria Farmacêutica, Atividades de Monitorização, Indicadores de Desempenho, Indicadores de Risco, Cartão do Centro

resumo

O presente relatório destina-se a reportar as atividades realizadas durante o estágio curricular na Novartis Farma Portugal, no âmbito do Mestrado de Gestão em Investigação Clínica, realizado entre outubro de 2020 e maio de 2021. Durante o período de formação, a estagiária desempenhou funções multidisciplinares inerentes às diferentes funções da equipa de monitorização de estudos clínicos. Para além disso, a estagiária elaborou um *site card* com base na seleção de indicadores de risco e desempenho, visando não só avaliar, mas também traduzir a qualidade operacional dos centros. Face ao atual estado da investigação clínica em Portugal, este documento aliado ao empenho e compromisso de todos os intervenientes poderá contribuir para o desenvolvimento da investigação clínica em Portugal.

keywords

Internship, Clinical Research, Pharmaceutical Industry, Monitoring Activities, Key Performance Indicators, Key Risk Indicators, Site Card

abstract

Included in this report are accounts of an internship undertaken at Novartis Pharma Portugal in the fulfilment of the Master of Clinical Research Management degree. During the training period, the intern performed multidisciplinary tasks covering the different functions performed by the members of the trial monitoring team. Additionally, the intern selected performance and risk indicators to not only reflect but also assess the operational quality of national sites through the creation of a site card. In face of the current state of clinical research in Portugal, the site card supported by the commitment of all stakeholders could contribute to further clinical trial development in Portugal.

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Abbreviations

AB - Administration Board

AE - Adverse Events

ALCOA^{+} - Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available

CA - Confidentiality Agreement

CEC - Competent Ethics Committee

CEIC - *Comissão de Ética para a Investigação Clinica*

CES - National Ethics Committee for Clinical Research

COV - Close-out Visit

CRA - Clinical Research Associate

CRF - Case Report Form

CRO - Contract Research Organization

CSM - Clinical Study Manager

CT - Clinical Trial

CTA - Clinical Trial Agreement

CTA - Clinical Trial Application

CTA - Clinical Trial Assistant

CTDTS - Clinical trials drug transmittal sheet

CTs/M - Submitted CTs per million inhabitants

CV - Curriculum vitae

DBL - Database lock

EDC - Electronic Data Capture

eTMF - electronic TMF

FA - Financial Agreement

FPFV - Fist Patient First Visit

GDD - Global Drug Development

GDO - Global Drug Operations

HA - Health Authority

IB - Investigator Brochure

ICF - Informed Consent Form

ICH-GCP - International Conference on Harmonization - Good Clinical Practice

IRB/IEC - Institutional Review Board/Independent Ethics Committee

I&D - Innovation and Development

IMP - Investigational Medicinal Product

ISF - Investigator Site File

KOL - Key Opinion Leader

KPI - Key Performance Indicators

KRI - Key Risk Indicators

LPFV - Last Patient First Visit

LPLV - Last Patient Last Visit

MVR - Monitoring Visit Report

MOV - Monitoring Visit

NHS - National Health Service

PD - Protocol Deviation

PI - Principal Investigator

RBM - Risk-based Monitoring

RNEC - National Registry for Clinical Studies

SAE - Serious Adverse Events

SC - Study Coordinator

SCR - Screen

SDR - Source Document Review

SDV - Source Document Verification

SIV - Site Initiation Visit

SoC - Study Medication and Standard of Care

SOP - Standard Operating Procedure

SSV - Site Selection Visit

TA - Therapeutic Area

TMF - Trial Master File

TMO - Trial Monitoring

TOC – Table of Content

WP - Working Practice

Chapter I

1. Introduction

The present curricular training report was elaborated under the scope of the second year of the master's degree in Clinical Research Management, summarizing the activities developed during the training period at Novartis Pharma Portugal affiliate, in Lisbon, from 12th October to 30th May of the current year.

In general terms, this report will address the vision about the institution where the training period took place, a theoretical contextualization on the Clinical Research, and on industry-initiated clinical trials, followed by the training objectives proposed. After that, there is a description of the developed activities in every training area, the current state of the art in clinical research in Portugal, the influential factors in the allocation of clinical trials by the pharmaceutical industry, as well as risk-based approach. As part of the internship, a special project was entailed to the intern. For the creation of site cards, metrics were selected to not only reflect but also assess the operational performance of national sites. Lastly, it is presented an assessment of involved risks in the internship, a brief discussion of relevant aspects of the training period, as well as the conclusions collected.

1.1. Vision on the Institution

Novartis is a global healthcare company, founded in 1996, based in Basel, Switzerland. As a leading global medicines company, Novartis aims to reimagine medicine to improve and extend people's lives, reaching nearly 800 million people. In 2019 Novartis not only had the largest pipeline, with 219 drug candidates, but also the largest number of originated drugs (131)[1].

Novartis is composed by two divisions: Innovative Medicines (innovative patent-protected prescription medicines) and Sandoz (generic pharmaceuticals and biosimilars). Novartis further splits its Innovative Medicines division into two global business units: Novartis Oncology and Novartis Pharmaceuticals focused on Ophthalmology, Neuroscience, Immunology, Hepatology and Dermatology, Respiratory, Cardiovascular, Renal and Metabolism and Established Medicines.

Of note, Novartis Pharmaceuticals also includes Novartis Gene Therapies, which develops gene therapies for patients with life-threatening neurological genetic diseases.

Global Drug Development (GDD) is the Novartis organizational unit that oversees the clinical development of new medicines that showed promising safety and efficacy results at early stages of research. Global Development Operations (GDO) is a centralized global function of GDD organization, that ensures treatments are tested safely and in line with health authority (HA) requirements[2].

1.1.1. Trial Monitoring

Integrated in GDD the Trial Monitoring (TMO) unit is responsible for conducting clinical trials (CT) at global and country level within agreed timelines and budget. At the local level, the execution of CTs is focused on trial feasibility, site selection, initiation, and monitoring alongside the management of participants' recruitment. Moreover, the TMO team also guarantees compliance of study site stakeholders and monitors sites to deliver high quality data in accordance with legislation and International Conference on Harmonization - Good Clinical Practice (ICH-GCP) guidelines. Currently, Portugal has a Country Monitoring Head (1), that is managing outsourcing services under several activities: Clinical Study Manager (CSM), Clinical Operations Lead, Clinical Trial Assistant (CTA), and Clinical Research Associate (CRA), and CRA Manager functions.

1.2. Clinical Research

Clinical Research is a patient-oriented research that aims on achieving a better understanding of health by addressing relevant scientific and health care questions. The development of knowledge and new treatments for better health and care becomes possible with the establishment of safety and effectiveness of specific health and medical products and practices. Traditionally, clinical drug development is divided into four temporal phases (Phase I-IV).

Clinical studies involve research using human volunteers intended to answer clinical questions and find better ways to treat or prevent illness, through development of innovative medicines or devices[3].

There are two major study designs categorized by the role of the investigator: interventional, and observational. During observational studies, investigators document a naturally occurring relationship between the exposure and the outcome. Participants are not assigned to specific interventions, and the exposure has already been decided naturally or by some other factor[4]. In interventional studies, also known as CTs, subjects are assigned to one or more interventions (e.g., drug or vaccine, diagnostic, therapeutic procedure, among others) to evaluate the effects of exposure on health related biomedical or behavioural outcomes, providing the strongest evidence in support of cause-effect relationships. CTs play a crucial role in the practice of evidence-based medicine and health care reform. Thus, promoting access to a variety of effective therapies to individual patients but also improving the value of health care provided to society[3].

1.2.1. Clinical Trials Stakeholders

The institutional Review Board/Independent Ethics Committee (IRB/IEC) safeguards the rights, safety, and well-being of trial subjects. The conduct of clinical trials in Portugal requires prior authorization from INFARMED, and favourable opinion of the Competent Ethics Committee (CEC). As set out in Decree-Law No. 21/2014 of April 16th, for both interventional clinical studies of medical devices and clinical trials the CEC is “Comissão de Ética para a Investigação Clinica” (CEIC), the National Ethics Committee for Clinical Research, unless it designates a local ethics committee for health (CES). As for the remaining studies, the CEC is the CES of the investigation site, unless the site involved does not have an ethics committee, and in this case, the CEC is the CEIC or, alternatively, other CES designated by CEIC[5].

The pharmaceutical industry undertakes the role of **sponsor**, which entails initiation, management, and financing of clinical trials. Before initiating a trial, the sponsor applies to the appropriate authorities for trial review and approval. After the trial design and requirements are defined, the sponsor proceeds to the site selection according to both investigator's qualification and adequate resources. After this, the financial aspects of the trial are documented in an agreement. In

multicentre trials, the sponsor also determines the choosing of a coordinating investigator. The sponsor is responsible for the proper conduct of the trial, assuring quality and complying with GCP and applicable regulatory requirements throughout the trial lifespan. Each trial must not only ensure human subject protection but also reliability of trial results.

Field Monitors are appointed by the sponsor and act as the main line of communication between the sponsor and the investigator/site. These stakeholders are required to have the scientific and/or clinical knowledge and adequate training to guarantee that the trial is conducted and documented properly in each and every site involved. The monitoring activities require that field monitors verify:

- The written informed consent is obtained prior to any subject activity in the trial
- The investigational product circuit
- If the qualifications and facilities remain adequate throughout the trial
- Whether all adverse events are reported within the required time periods
- The correct data is collected through the review of the accuracy and completeness of the Case Report Form (CRF) entries.

In the event of the sponsor transferring either partially or fully its own duties to a Contract Research Organization (CRO), the sponsor remains ultimately responsible for the integrity and quality of data.

The **investigator** is responsible for the oversight of the conduct of the clinical trial in compliance with GCP, applicable legislation and protocol requirements at the site and can act as the leader of the team assuming the position of principal investigator (PI). Therefore, the investigator's main activities focus on obtaining and documenting the informed consent prior to any subject's participation in the trial, maintaining adequate and accurate source documents and trial records, ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Furthermore, the investigator must report the occurrence of adverse events (AEs), not mentioned in the protocol or other document, immediately to the

sponsor and providing adequate medical care during and following a subject's participation in a trial[6].

The **Study Coordinator** (SC) manages multiple trials at the site under the supervision of the PI, SCs assist during the scheduling and management of participant visits and assessment requests and maintain clinical data and notify the sponsor, through the monitor, about the subject's expenses related to their participation in the trial[7]. The **study site** is the location provided with human and physical resources where trial-related activities are conducted. The administration board (AB) decides if the conduct of the CT will take place on its premises and must come to a consensus with the sponsor in the execution of the financial agreement (FA).

Clinical trial **participants** are the initial providers of data to investigators and sponsors. Without patients or healthy volunteers, CTs would not take place, and consequently advancing science and improving clinical care would not be possible[6].

1.2.2. Industry Initiated Clinical Trials

In 2018, an estimate of 1.36 percent of Portugal's Gross Domestic Product was spent on innovation and development (I&D), reaching the highest expenditure in I&D in 2009 (1.58%). According to the European Commission, in 2016, the pharmaceutical industry was the largest investor in I&D worldwide[8]. Of note, Novartis alone invested 8.5 billion euros in I&D between 2016 and 2017. Investment in clinical research by the pharmaceutical industry has a profound impact on the socioeconomic sector. Industry-sponsored clinical trials represent a source of funding for the National Health Service (NHS), as they reduce public expenditure and contribute to the long-term sustainability of the NHS. In 2017, CTs had an estimated impact of 87 million euros, meaning that for each euro invested in the activity it was obtained a return of 1.99 on the Portuguese economy (199%)[9].

The high cost associated with I&D has caused industry to move in the direction of emerging markets. In 2018 the distribution of trials by therapeutic area (TA) revealed the dominance of oncology, followed by Autoimmune/Inflammatory,

Metabolic/ Endocrinology, Central Nervous System, Cardiovascular, among others[10].

Through the years, industry has clearly demonstrated high quality regarding the way to conduct study preparation, ethics committee submission, and the quality of data monitoring. Therefore, the financial strength aligned to an integrated infrastructure of people with expertise in several fields lead the pharmaceutical industry to important therapeutic advances[11].

2. Training Objectives

The training plan included a multidisciplinary experience focused on the local clinical trials unit at Novartis Portugal.

The main objectives for this internship were:

- Acquire inside knowledge related to monitoring of clinical trials conducted by a pharmaceutical company;
- Identify the organizational structure of Global Drug Development Division;
- Understand the workflow, responsibilities and impact of the TMO team stakeholders;
- Apply and train the theoretical knowledge acquired during the master's course, enabling a smooth relationship between the output of education and the contact with real work market;
- Develop important teamwork skills and good interpersonal relationships among the company's colleagues;
- Obtain specific working tools and techniques that aid in developing the proposed tasks in a precise, careful and successful way;
- Identify areas of interest within pharmaceutical research.

3. Activities

The first month was highly dedicated to Novartis training courses, which comprised standard operating procedures (SOPs) as well as working practices (WPs) regarding not only the company's workflow but also monitoring of clinical trials (table 1).

Table 1 *Training courses completed during the first month of the curricular internship.*

Training Transcript
Navigating through Novartis Systems
TMO Onboarding CRA
Qualification and Training of GxP Personnel (Global)
Quality Issue Management
Onboarding Patient Safety
Onboarding Quality
Annual training in pharmacovigilance
Refresher on GCP, Local regulation and SOPs
Data Integrity Foundational Training
Risk Based Monitoring
Global Quality Assurance

The following months provided the intern a broader perspective of the working environment, allowing the execution of multidisciplinary tasks covering the different functions performed by the members of the TMO team (table 2).

Table 2 *Summary of activities performed during the curricular internship.*

Clinical Trial Submission	Elaboration and submission of a dossier to request interventional study authorization from site's administration board
Substantial and non-substantial amendments	Elaboration and submission of two dossiers to request substantial amendment favourable opinion from CEIC via RNEC
CEIC notifications	Site Initiation Visit (SIV); First Patient First Visit (FPFV) and Close-out Visit (COV)
Financial Agreement	Elaboration of a National Coordinator Financial Agreement

	Elaboration of a Clinical Trial Site Agreement
	Elaboration of a Service Provision Agreement
Trial Master File (TMF)	TMF Review
	Import documents into electronic TMF (eTMF)
Monitoring Activities	Participation in two remote SIVs
	Participation in four on-site Monitoring Visits (MOV)
	Participation in two remote COVs
Pocket guide	Construction of a pocket guide
Annual Progress Reports	Elaboration of one initial report
	Elaboration of several follow-up reports
Investigational Medicinal Product (IMP) labels printing	Documents assembly for IMP labels printing
Study Participation Certificates	Elaboration of Study Participation Certificates
Site Card	Selection of performance indicators
	Site Card construction
	Data and sites performance assessment

3.1. Clinical Trial Submission

Clinical trials are currently regulated by the Regulation (EU) No 536/2014 of April 16th, which provides for the authorization from a competent authority and a positive opinion from a central ethics committee prior to the conduct of the trial in a given Member State. Therefore, in Portugal, the clinical trial applications shall be submitted to both INFARMED, and CEIC through National Registry for Clinical Studies (RNEC) portal, according to the applicable legal requirements and after payment of the applicable fee through the gateway provided by the RNEC platform. RNEC is a tool for registry and publication of all clinical studies undergoing nationally, allowing for a better interaction with all the stakeholders.
Interventional studies require 3 authorizations to initiate: INFARMED, CEIC, and the site's AB.

3.1.1. Request interventional study authorization from site's administration board

During the internship, a dossier to request study authorization from a selected site's AB was prepared. Documentation can be sent electronically or in paper to the site, depending on the preference of the AB. Novartis has an index that lists all the documentation needed for the authorization request. However, the site may have its own template, or require the inclusion of specific documents and, in this case, Novartis adapts the information according to the site's requirements.
In line with the above, the intern assisted in the elaboration of **one** dossier for the initial submission, composed of the documents presented in figure 1. The completed dossier was sent electronically, as requested by the site.

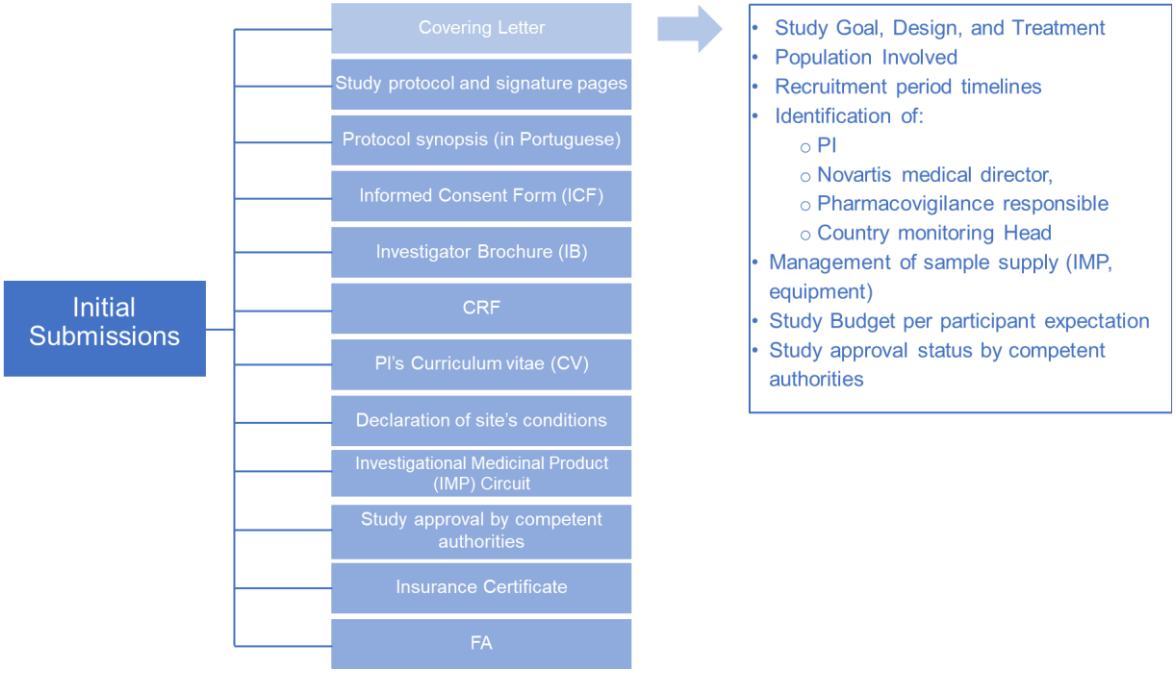

Figure 1 *Documents required for the validation of new trials.*

Even if the submission folder is sent electronically, the paper version of the financial agreement is always sent to the site in order to collect all the required signatures. Commonly, the financial agreement is tripartite, meaning that it is signed by the Sponsor, Site AB and PI and also that there are 3 copies of the document that once signed are to be kept one at the investigator Site File (ISF), one at Novartis, and the last one with AB. In general terms, the SC streamlines the process of collecting signatures from those involved in the site.

3.2. Substantial and non-substantial amendments

After the beginning of the trial, the sponsor may apply substantial amendments that likely update information or requests of either one of the following aspects:

- Safety or physical or mental integrity of the clinical trial participants
- Scientific value of the trial
- Conducting or managing the trial
- Quality or safety of any IMP used in the trial

Such amendments require authorization from INFARMED, and/or a favorable opinion from CEIC before its implementation, depending on the impact of change. If the authority does not require the impacted changes review, they should still be notified. These substantial amendments are also managed via RNEC portal for all trials initially submitted via RNEC and in paper for studies that started with the previous paper process submission.

Two requests for a substantial amendment favorable opinion were made to CEIC via RNEC. To comply with regulatory requirements, each request includes the documents presented in the following figure (figure 2).

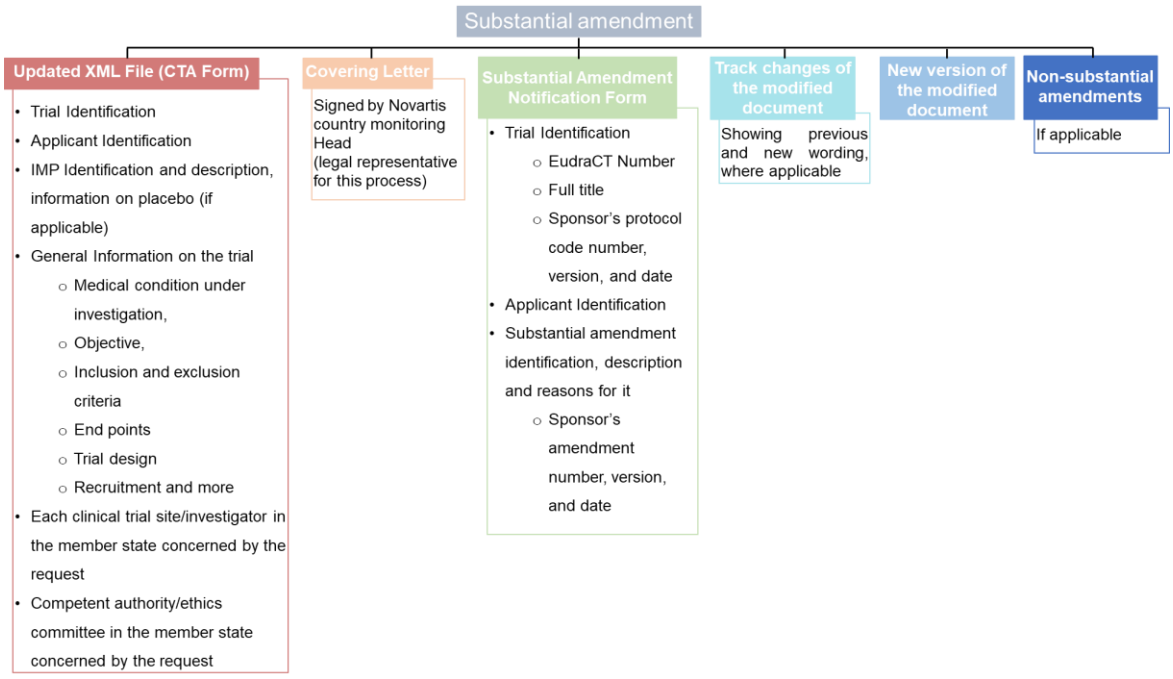

Figure 2 *Documents to be included in requests for substantial amendment favorable opinion.*

Directive 2001/20/EC does not require notification, nor immediate submission of information of non-substantial amendments. The sponsor should record any non-substantial amendments and later submit together with documentation, such as substantial amendments.

3.2.1. Request substantial amendment favorable opinion

The intern assisted the CTA responsible for submissions, in the elaboration of **two** dossiers to be submitted via RNEC for CEIC's favorable opinion. The first request included both substantial and non-substantial amendments. Thus, a new version of the pregnancy follow-up consent form (substantial amendment) was submitted together with an updated version of the IB (non-substantial amendment) (figure 3).

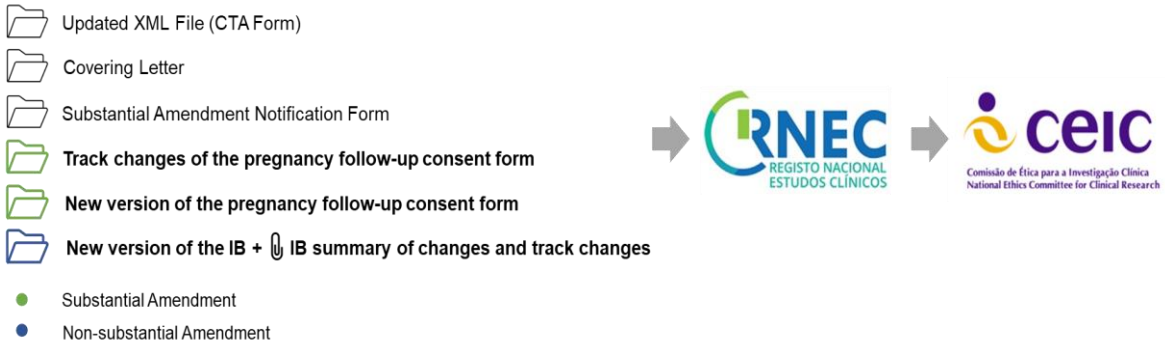

Figure 3 *Documents gathered to request CEIC's favorable opinion via RNEC portal for both substantial and non-substantial amendments.*

In addition to the aforementioned request, a change of PI was also submitted as substantial amendment, as it directly affects the conduct and management of the trial (figure 4).

Figure 4 *Documents gathered to request CEIC's favorable opinion via RNEC portal for substantial amendment.*

3.3. Notifications

Through the study lifespan local legislation demands that, CEIC must be notified via RNEC portal of the following event dates for each site, presented in figure 5.

Figure 5 *The event dates to be notified to CEIC via RNEC portal.*

LPFV Last Patient First Visit; LPLV Last Patient Last Visit.

These notifications only include a covering letter, except for the LPLV that also attaches a declaration of the end of the trial form. For both national and global levels, the same form is applied, changing the filled-in fields. Whenever possible several study sites' event dates are assembled in the same notification.
The intern aided the CTA in the preparation of the documents requested to notify the following event dates via RNEC portal: **SIV**, **FPFV** and **COV**.

3.4. Financial Agreement

The sponsor must have a financial agreement, clinical trial agreement (CTA), with each participant trial site. During the internship, it was possible to support the contract specialist in preparing a multi-party agreement. Thus, **4 FAs** were prepared: national coordinator, both site minute, and Novartis minute, and service provision.

3.4.1. Elaboration of a National Coordinator Financial Agreement

Multicenter clinical trials include a national coordinator responsible for supporting the scientific and ethical value of the study. The national coordinator is often a Key Opinion Leader (KOL) that assists its peers during the identification and

referencing of participants. Therefore, an agreement between the sponsor, the institution, and this collaborator must be settled.

As set out in Decree-Law No. 21/2014 of April 16th, whenever the investigator, PI, or other study member is a NHS worker, the remuneration provided in the FA must be paid by the study site. Novartis may directly pay the national coordinator if the latter works in a site that does not participate in the clinical study[5].

In this case, the national coordinator undertook simultaneously the role of PI in one of the trial sites, hence the institution's inclusion in the FA. Occasionally, national coordinators waive the direct payment attributed to this function, as they will already be paid for performing the PI's duties.

The intern supported the contract specialist during the elaboration of the agreement. This document described the national coordinator responsibilities. Of note, the national coordinator waived the payment attributed to this function as PI's duties were already being performed. For this reason, the document did not include the total amount to be paid, distributed per milestones reached.

3.4.2. Clinical Trial Site Agreement

The financial agreement describes the regulatory requirements and the stakeholders' responsibilities. The typical parties to a CTA negotiation should be the institution, PI, and Novartis.

The financial agreement addresses several topics applicable to different studies (e.g., confidentiality, publication, intellectual property, among others). During the execution of the FA, the following topics vary according to the study of interest:

- Site information (institution, PI)
- Study general information (study title, IMP)
- Payment clause (study design, costs associated to visits, exams, payment requests)
- Compassionate use

In case the site requires any clause adjustment, Novartis legal department must intervene to reach a consensus with the institution. This implemented practice guarantees that there are no legal impacts on the change.

3.4.2.1. Elaboration of a Clinical Trial Site Agreement

The intern participated in the elaboration of a site's FA. The calculation of the study budget per category and participant was based on the economic memory and site's conditions. The total amount to be paid to the institution and the remaining fund directed to the investigation team were calculated as shown in figure 6.

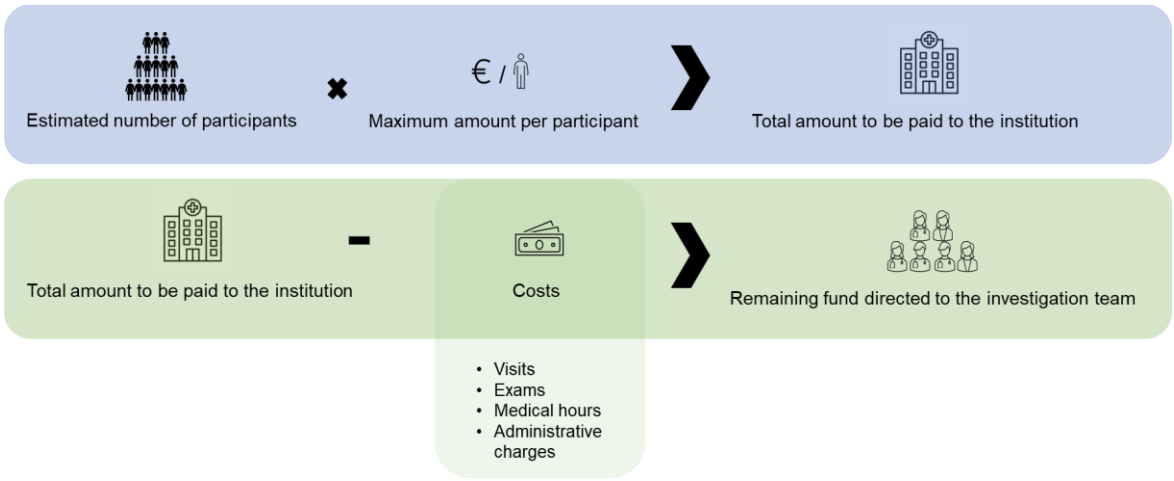

Figure 6 *Calculation of both the total amount to be paid to the institution and the remaining fund.*

The distribution of the study budget per category is shown in the following table (table 3):

Table 3 *Distribution of the study budget per category.*

Estimated participants visits					
Visit	Exams	Medical hour	Administrative charges	Remaining	Total per visit

Protocol exams foreseen					
Visit	Exam code	Description	Price (fees not included)	Quantity	Total per participant

Additional assessments foreseen in the protocol

Visit (if clinically indicated)	Assessment code	Description	Price (fees not included)

Screening (SCR) Failure Costs

Visit	Exams	Medical Hour	Administrative charges	Remaining	Total per visit

Extra Cycle/Visit costs

Visit	Exams	Medical Hour	Administrative charges	Remaining	Total per visit

Unscheduled visits costs

Visit	Exams	Medical Hour	Administrative charges	Remaining	Total per visit

In addition to the total charge per participant, there may be extra payments for protocol foreseen exams when clinically indicated.

If the participant does not complete the study, the amount to be paid is calculated based on the attended visits. Thus, SCR failure costs are based on the values defined for the respective visits and the exams/procedures performed. Despite being mentioned in the agreement, the example reviewed during this exercise requested a description of SCR failure costs.

This protocol included additional treatment cycles, therefore a description of the values for each possible extra cycle/visit was also included.

Furthermore, this site required the use of their own FA template in parallel with the Novartis FA minute. The site's FA minute included the study team, and the values (%) to be distributed to each member according to the PI's proposal.

3.4.3. Elaboration of a Service Provision Agreement

During the training period, the intern supported the contract specialist in the service provision agreement preparation. Sites may not have access to all the necessary assessments required by protocol or its timeline requests for the study, thus, external services aim to assist sites by meeting their needs during the conduct of the trial.

The PI indicates the expected service provider to be reached and an agreement is established between Novartis, and the external clinic, describing the responsibilities and the costs for the foreseen exams (table 4):

Table 4 *Distribution of service provision budget per category.*

Exam price list			
Exams	Price	Number of foreseen exams per participant	Total

Participants are directed to the external clinic to perform the complementary diagnostic assessments, being the results sent afterward directly to the site. The site manages all participant information directly with the external clinic and in this case, the sponsor pays the external service for the exams performed.

3.5. Archiving and Review of Trial Master File

The TMF should contain the essential documents to be filed at the sponsor and the institution, allowing confirmation of the clinical study procedures and processes and the quality of the data produced. The TMF is usually composed of a sponsor TMF, held by the sponsor, and an investigator TMF, often referred to as the ISF. Both TMFs have different contents due to the different nature of responsibilities of the site and sponsor[12]. In Portugal, the management of all IMP circuit information is entailed to the Pharmacy Department and usually has what is called a Pharmacy File, which composes the Investigator File.

Essential documents demonstrate the compliance of the investigator, sponsor and CRA with the standards of GCP and applicable regulatory requirements.

Every line function from the study team is accountable for the accuracy and completeness of the TMF. The CSM must maintain and update the respective TMF at country level and the CRA is entailed to maintain and update the respective TMF at site level. From site selection, to close out, the CRA collects copies of the documents from the site on an ongoing basis, as originals are to be stored at the site. After collection, paper scanner or eTMF PDF documents must be imported to sponsor eTMF into specific site, country, and study TMF folders, within 30 working days. By the time, a COV takes place, the CRA ensures that all

the documents are current, finalized and have been correctly imported. A high-quality TMF is based on 4 key principles (figure 7):

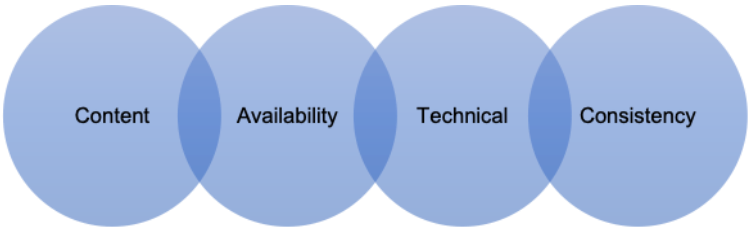

Figure 7 *Key Principles for a high-quality TMF.*

All required and expected documents should be available at a given time and individually have high quality content with the right attributes (accuracy and completeness)[12]. Documents should be filed in the appropriate folder within the archive system (accessible whenever needed).

Figure 8 presents the filing principles that should always be applied when scanning and importing documents.

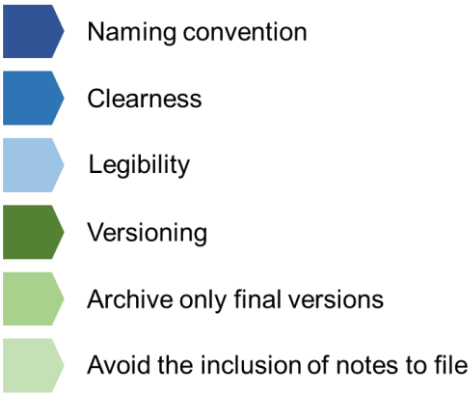

Figure 8 *Filling principles for scanning and importing documents.*

Imported documents must be consistent between documents that may apply to. For instance, the training log must match the delegation and signature log while the documents are reviewed, as the names required in the training log are also noted on the delegation and signature log (consistency).

Therefore, the electronic document management system allows Novartis to handle all clinical developments' documentation in a standardized way. The eTMF

facilitates efficient retrieval of information and should be the official source for any audits, inspections, and submissions developed.

Performing a TMF review is a necessary quality control activity to maintain a high quality TMF for each trial and have study inspection ready. To perform this task, Table of Content (TOC) reports may be used to support the review. The available virtual TOC helps users to manage TMF documents, by tracking their availability, locating documents stored in other repositories and allowing HA to inspect and access TMF documents through a master list section. Ideally, TMF review should be performed every 6 months. The person responsible for TMF review at the site level is the CRA. However, this task can be time-consuming, and considering the CRA tight schedule, it may become complicated to perform the review by the deadlines set and so it can be delegated to other TMO associates always under CRA responsibility.

The electronic filing cabinet has a tree structure, displaying all the countries that are participating in the trial and presenting documents per country and site. The documents included in the country folder differ from the ones in the site folder. The TMF documents listed below (table 5) individually and collectively permit the evaluation of the quality of data produced and the assessment of the conduct of clinical trials at a site level. Of note, the table below shows the documents that in general terms correspond to the TMF site's folder, however, they may vary depending on the conditions of the study and site.

Table 5 *TMF Master List at site level.*

TMF Section Name	**Description/Purpose**
Site Specific TMF TOC Version	Initial TOC lists the availability and locations of documents.
CVs and Qualifications	CVs of study team.
Medical License and Training Certificates	GCP Certificates (applied to all study members) Electronic Data Capture (EDC) Certificates of understanding of study team (not applied to all study members).
Site Personnel Training Records	Effective protocol versions Study Procedures

	End of treatment visit procedures Covid-19 guidance, among others.
Financial Disclosures	Financial Agreement with PI and SIs. It may be applied to other study members, depending on the study.
Delegation and signature log (DSL)	Delegation by the PI of trial specific tasks to site personnel conducting the trial. To include updates.
Signed Protocol Signature Pages	Final Protocol signature page Amended Protocol Signature page
Signed Agreements	CTA Confidentiality Agreement (CA)
Local Laboratory Documents	Local Lab Certificates Local Lab Normal Values CV Local Lab Head
Site Additional Exams	Electrocardiogram Biopsy X-Ray Others
IB Distribution Log and Receipt Form	IB received by site(s) and effective versions
Recruitment and Selection	Selection and Facilities Report Site Selection Visit (SSV) Report Site Feasibility Documents Declaration Site Conditions Pharmacy Declaration IMP Circuit
Monitoring	SIV Report Source Data Agreement Form Contact Report Form electronic Monitoring Visit Report (MVR), Remote MVR Handover Reports COV Report

	Field Monitor Responsibility
Monitoring Agenda Letter and Follow up letter	Monitoring visit dates and attendees (including e-mails), site's compliance evaluation (critical issues)
Financial Agreements including payments	Invoice Request
Trial Medication (Collected at the end of the study)	Shipping/Delivery Records Drug Accountability Log Return and Destruction Record Temperature Log
Correspondence	Investigator Notification Correspondence e-mails between Investigator and Sponsor headquarter e-mails between Investigator and Sponsor Local Country Pharma Organization

As aforementioned, the person responsible for TMF review at the site level is the CRA. Therefore, the intern performed several reviews for different clinical studies strictly complying with the deadlines, while under supervision of the CRA responsible for the specific site.

Importing documents into Novartis' eTMF may take a substantial amount of time. Of note, the intern assisted CTAs during the performance of such tasks, thus greatly decreasing the heavy workload inherent to this function (table 6).

Table 6 *Summary of actions taken during TMF Review and importing documents into eTMF.*

Task	**Action**
TMF Review	Review and update, if necessary, the list of available TMF documents
	Take appropriate actions for missing, misfiled, or incomplete documents
	Ensure all relevant versions for a given document are available
	Guarantee consistency across documents, by checking reconciliation between different types of documents
Import documents into eTMF	Apply the filling principles

3.6. Monitoring Activities

Monitoring oversees the progress of a clinical trial ensuring the proper trial conduct, record, and report, in accordance with protocol, SOPs/WPs, GCPs and all applicable regulatory requirements. The CRA is responsible for verifying the completion and accuracy of data, safety of participants and protocol adherence. The number of MOVs performed varies according to the complexity of the study, rate of recruitment, and it may be adjusted as the study proceeds, especially if findings are detected (protocol deviations, issues). Regular site CRA visits can be broken down into four types: site selection, initiation, monitoring, and close-out visits.

Given the covid-19 pandemic, and the possible recurrence, there has been an increased demand for remote monitoring, given that in-person visits may represent an additional risk for a specific patient, and solutions for preserving trial integrity. Therefore, during the training period, monitoring was majorly performed remotely, as most sites suspended and limited their access.

3.6.1. Site Initiation Visit

SIV only takes place after due authorizations are granted and prior to site activation (first participant included) for a specific protocol. This kick-off meeting is performed by the CRA to ensure the protocol requirements are well known by all study stakeholders and that they know what their roles involve. After the meeting, the study staff should be fully prepared to conduct the clinical study according to the protocol and GCP guidelines. The project may be presented more than once, as it depends on the protocol and the study stakeholders involved, covering in each meeting specific topics that are adapted according to the public (e.g., pharmaceutical team, medical team, radiology team and more).

The intern participated in **two remote SIVs** within the scope of the same clinical study, aimed at different audiences. Therefore, the following table compares the topics covered during both SIVs performed for the medical team and the pharmaceutical team (table 7).

Table 7 *Differences between two SIV meetings conducted for the medical team and pharmaceutical team.*

Topic	Subtopic	SIV Study Team	SIV Pharma
Operational study status	Country recruitment status	x	x
	Timelines and recruitment target	x	x
Protocol Review	Study Design	x	x
	Primary Objective	x	x
	Key Inclusion and Exclusion Criteria	x	x
	Prohibited Medications During Study	x	x
	Discontinuation of Study Treatment	x	x
	Study Medication and Standard of Care (SoC)	x	x
	Patient Reported Outcomes	x	
	Clinician Reported Outcomes	x	
Study Treatment	Safety Summary Of IMP	x	x
	Mode of Action	x	x
IMP Handling Procedures	Transport/Distribution Excursion		x
	IMP Photos	x	x
	Storage Conditions		x
Study Vendors	EDC System	x	
	Interactive Response Technology System	x	x
Source data and trial monitoring requirements	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available (ALCOA^{+})	x	x
	IMP For Destruction		x
	Informed Consent Form	x	

	Temperature Registers		x
	Investigator File	x	
	Pharmacy File		x
	Accountability Log (both Master and Participant's)		x
Safety Reporting	AEs reporting	x	x
	Serious Adverse Events (SAE) reporting requirements	x	x
	Pregnancy Reporting	x	x
Publication Policy		x	
Expectations of Site's Performance	Key performance indicators	x	x
ICH-GCP	Review of main topics	x	x

3.6.2. Monitoring Visit

The conducting phase of the trial emphasis is placed on participant recruitment and retention, and monitoring data compliance, by performing source document verification (SDV)/Source Document Review (SDR) and review with site stakeholders that site processes are being correctly implemented. Regular contacts are held between CRAs and mostly study coordinators, to maintain ongoing communication in this phase. Individual calls allow not only sites to share personal experiences and build a sponsor-site-relationship but also CRAs to remotely oversight site activities. On-site-visits prove to be beneficial as it facilitates more targeted, in-depth discussions with site teams, however, the Covid-19 pandemic allied with technology evolution has promoted remote visits, also proving to be very effective.

In general terms, during a MOV, the CRA evaluates the following topics throughout the study:

- ICF
- Protocol and regulatory compliance
- Safety Information
- Qualifications, clinical operations, and resources of site
- Recruitment Status
- Source Documents review
- IMP

The CRF is the tool used to collect data from each participant, thus during MOV, the CRA verifies if critical data within CRF is in conformity with the source medical documents of the participant. For this, the CRA checks, for specific visits and data, missing visits, assessments, or procedures and if all the procedures performed are accurately documented. If medical records contain physician notes, assuring attribution of events correctly documented and if laboratory and procedure reports are reviewed (dated and signed) by the responsible person. Lack of information reported in the medical diary (e.g., intensity of adverse events) may be an indicator of PI's lack of oversight. Furthermore, CRA reinforces the need to resolve open queries, and the ISF must also be reviewed, identifying any missing document, namely CVs and GCP certificates, guaranteeing the completion of the training log that must register all the study members trained matching the start date documented in the Delegation Log. In case of new documents or updated versions included in the ISF, the CRA scans these to later import them into the sponsor's system.

Whenever possible, at the end of the visit, the CRA meets the PI to share findings and correct them if possible, and/or to access the procedures that need to be reviewed by site staff. After these visits, a monitoring report is prepared, and a follow-up email is sent to the site summarizing the topics covered during the visits and listing each action needed to be performed by whom and till when.

Remote MOVs were highly encouraged by the current Covid-19 pandemic, however there are specific tasks, such as medication accounting, that are only possible during on-site visits.

As there is the need to complete the IMP circuit, the IMP is returned for destruction when: not attributed to the participants, returned by participants (for not being used), and/or date expires, in order to have a certificate of destruction available. This process can also be done by sites however it increases the costs; hence it is often performed by the sponsor. During the accountability of medication, the following data is recorded in the Clinical trials drug transmittal sheet (CTDTS):

- Batch
- Expiration date
- Name and dose (mg)
- IMP code
- IMP quantity (e.g., 70 capsules)

The CTDTS must be signed by the pharmacist and CRA and a copy must be kept at the investigator/pharmacy file.

The sponsor sends extra medication enabling the site to react effectively and meet the site's needs that may arise during the study conduct, such as damaging or loss of IMP.

In case a study includes several IMP doses (e.g., several titrations) the sponsor must do efficient stock management, considering the number of participants involved, to minimize unnecessary expenses. Currently, this is performed using electronic systems.

During the training period, the intern accompanied different CRAs responsible for specific sites in **4 MOVs**, conducted **on-site**. One of the visits was conducted exclusively at the site’s pharmacy, performing the IMP accountability of two clinical studies. The following table presents the regions where the MOVs took place as well as the tasks performed during the visits (table 8).

Table 8 *Summary of tasks performed during 4 on-site MOVs and the respective region where visits took place.*

	Region			
Tasks performed during on-site MOV	Lisbon	Lisbon	Porto	Braga
Verify if critical data within CRF is in conformity with the source medical documents	x			
Resolve open queries	x		x	x
Review ISF	x		x	x
Resolve pending issues with study team	x			x
IMP accountability		x		x
Prepare the IMP and set the collection from the site for destruction		x		x
Review pharmacy file				x

3.6.3. Close out Visit

Site close-out takes place after LPLV at the site has occurred, after all study databases are cleaned and closed, and ensures all study related activities are completed appropriately in compliance with protocol, SOPs/WPs, GCP and local regulations. By the time, this visit occurs, all participant data review, required by monitoring plan, has been completed, queries and missing data have been closed and resolved and the applicable documents and databases have been signed by the PI, being then declared the database lock (DBL). Thus, per WP, COV must be conducted within 12 weeks of DBL.

The COV can be split into several meetings to cover specific topics with different site members. The intern participated in **two remote COVs** within the scope of the same clinical study, aimed at different audiences (PI and SC).

Hence, the visit conducted with the PI enabled the CRA to review specific required points that were documented in the close-out letter, signed by the CSM, CRA and later signed by the PI to document the review of its content. As the accompanied visit was conducted in a site that did not recruit participants, the close-out visit letter included the following topics:

- Archiving process and facilities
- ICF archiving
- Essential Documents, ISF
- Inspection’s requirements
- Financial Disclosure
- IMP Accountability
- Safety Information
- EDC
- Site’s payments
- Retention Policy
- Publication Policy

Of note, the safety information was not applicable to the site’s situation, as a participant follow-up would not be conducted (null recruitment rate). Similar to IMP, the return of supplies, such as equipment (e.g., scales, Electrocardiogram machine, tablets, laboratory kits) provided for the study, was also confirmed during COV. Lastly, the CRA instructed the PI to complete the delegation log, by filling the study members end dates.

During the meeting with the SC, ongoing monitoring issues had been addressed and resolved. Thus, the topics covered were the following:

- Delegation Log reviews (pages and dates) against further documents
- CVs of all site staff that participated in the trial
- Participation certificates
- Effective Protocol versions archived
- Effective IB versions archived and/or documented
- Effective ICF versions archived

3.7. Pocket guide

The pocket guide is a document that summarizes the most relevant information for participants' recruitment, supporting the study team to correctly apply the protocol requirements.

During the training period, a specific site' study team requested the CRA for a pocket guide to assist the study staff during trial conduct. Thus, the CRA delegated the creation of the document to the intern.

Even though being frequently used as a triptych version, this document does not have a defined structure, as it depends on the protocol and occasionally the requirements of the PI. The information assembled in the pocket guide comes from the protocol and study synopsis.

Therefore, considering the variance of information displayed in the Pocket Guide, the content of the document may include the following topics:

- Study Design
- Key Inclusion and Exclusion Criteria
- Assessment requirements
- Prohibited medication
- Recommended Administration of Standard Care
- Adverse events and SAEs reporting
- Patient discontinuation, lost to Follow-Up and premature participant withdrawal requirements
- Study assessments/information to be recorded
- Study Title
- Contact details (Study CRA and pharmacovigilance team)

3.8. Annual Progress Reports

As set out in Decree-Law No. 21/2014 of April 16th, the CEC is responsible to monitor the study, focusing on the ethical aspects, ensuring the safety and well-being of the participants. Sponsors should send an annual progress report

enabling continuous monitoring of the study lifespan by the CEC. The initial report must be submitted one year after gathering all the necessary authorisations required by law for the study and as the study progresses, a follow-up report must be submitted every year. This document does not present any notifications, nor minor amendments, including only substantial amendments. Depending on the study, whenever versions are updated, these must be included in the follow-up report. Protocol, IB(s), and ICF(s) versions are frequently updated, different ICFs may be applied for different purposes (e.g., ICF pregnant participant follow-up, pregnant partner follow-up), and as substantial amendments, these must always be included in the follow-up reports. The following table displays the content evaluated each year by the CEC (table 9).

Table 9 *Annual Progress Report content.*

Topic	**Subtopic**
Study Information	EudraCT Number
	Protocol Number
	Study Title
	Sponsor
	Applicant for Portugal
	National Coordinator
Study Details	Protocol Effective Version
	Informed Consent Form(s) Effective version(s)
	Investigator Brochure(s) effective version(s)
	CEC Initial Positive Opinion Date
	INFARMED Initial Authorization Date
	National Commission for Data Protection Initial Authorization Date
	Insurance Certificate expiry Date
Substantial Amendments	Description of substantial amendment
	Authority
	Positive Opinion/ Authorization Date
	Site(s) Implementation Date

Site Information	Study Site Number Site Name PI Name CEIC Financial Agreement Approval Date SIV Date FPFV Date Total Number Included Participant(s) Total Number Randomized Participant(s) Total Number SCR Failures Total Number Completed Treatment Participant(s) Total Number Dropped Treatment Participant(s) Dropped Treatment Date (Participant Nr.) LPLV Date COV Date
Protocol Deviations	Study Site Number Minor Protocol Deviation (PD) Number
Medical Team	Study Site Number New staff Left the team
Attachments	Study Site Number Subject Number Visit Name PD Code Protocol Deviation List of Sites in Portugal

Of note the following event dates are only applied to the initial report: CEC initial positive opinion, INFARMED initial authorisation.

During the training period, the intern elaborated **one initial report** and **several follow-up reports**. The subtopics provided in follow-up reports often undergo yearly changes. Notwithstanding, the updates on these reports are listed in the table provided below. In the event a site was still conducting recruitment, the applicable subtopics (e.g., the total number of randomized participants) covered in the site information section were updated as well (table 10).

Table 10 *Subtopics that often undergo yearly changes and must be updated and included in the follow-up reports.*

Topic	Subtopic
Study Details	Protocol Effective Version
	Informed Consent Form(s) Effective version(s)
	Insurance Certificate expiry Date
Substantial Amendments	Description of substantial amendment
	Positive Opinion/ Authorization Date
	Site(s) Implementation Date
Protocol Deviations	Study Site Number
	Minor Protocol Deviation (PD) Number
Attachments	Study Site Number
	Subject Number
	Visit Name
	PD Code
	Protocol Deviation List of Sites in Portugal

3.9. IMP labels printing

During the study, the CRA manages the IMP supply according to the needs of the sites. For this, the request must be made to the warehouse facility (a third party) that locally stores, releases, and distributes the IMP purchased by Novartis. For the drug to be released, the production of labels must be performed in order to document that this IMP will be used on this specific study. To streamline the request process, the TMO team takes care of the documents needed for IMP printing labels. During the training period, the intern was responsible for the performance of this task as delegated by the Clinical Operations Lead.

In general terms, the data required for IMP labeling are (whenever they are not already included in the IMP box):

- Packaging control number
- Batch
- IMP Expiration date

- IMP name
- IMP form (e.g., capsule, implant)
- IMP dose (e.g., mg)
- Conservation Temperature
- Packaging and Labelling Specifications

When requesting the warehouse to produce the labels the following information should also be sent to the warehouse:

- Total number of packages ordered
- Number of printed labels

The number of printed labels will be the total number of packages ordered+2. The two extra labels are the first and the last to be printed, corresponding to quality samples.

3.10. Study Participation Certificates

Several site team members request a certificate proving their participation in a study either ongoing or concluded, sponsored by Novartis. Details about the participation in investigators' meetings may also be included in the certificates, if applicable and requested.
During the training period, the intern assisted the CTAs in the elaboration of certificates. The following list presents the information needed for the certificate:

- Name
- Site Name
- Protocol Number
- Study Name
- Study Title
- EudraCT Number
- Study Role

- Study Start Date
- Study End Date, if applicable

Chapter II

1. Clinical Research in Portugal

Regarding the number of commercial and non-commercial CTs submitted, Portugal has shown through the years a similar pattern to the one seen in Europe in general. Since 2006, commercial CTs have shown dominance over the non-commercial, varying from 89%-96%, contrasting to 4%-14% of the non-commercial CTs submitted (figure 9).

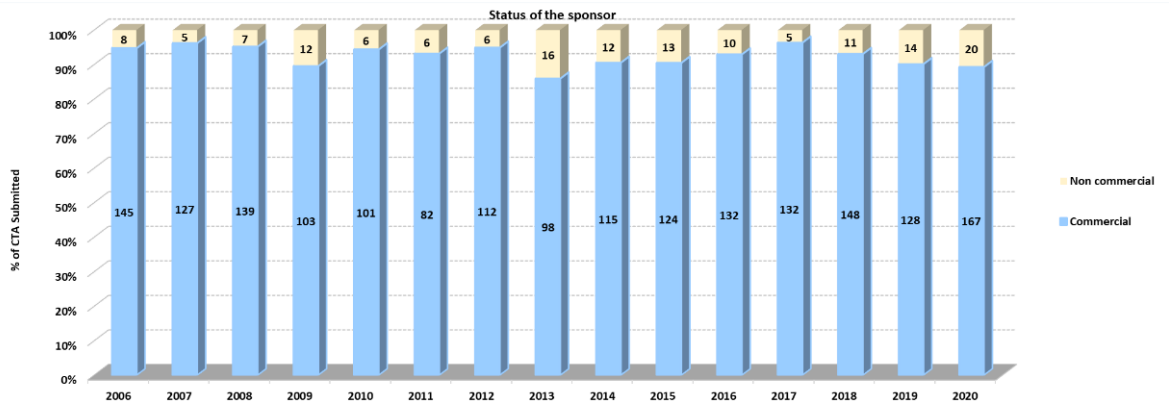

Figure 9 *Number of commercial and non-commercial CTs submitted per year in Portugal (from https://www.infarmed.pt/web/infarmed-en/human-medicines/statistics-of-clinical-trials-assessed-by-infarmed).*

Despite the recognized benefits of clinical research, some barriers may hamper the development of CTs in Portugal. Moreover, the highest recorded value was in 2006 with 15.2 submitted CTs per million inhabitants (CTs/M). Strikingly, recent years have yet to achieve the values reported in 2006. Of note, the number of registered clinical trials has been steadily rising reaching 13.3 submitted CTs/M in 2017 (figure 10). It should be noted that 2020 presents a value of 18.3 submitted CTs/M, largely exceeding the value registered in 2006 (160 to 187). Yet, this value should be considered atypical since it reflects the covid-19 pandemic, started in 2020[13].

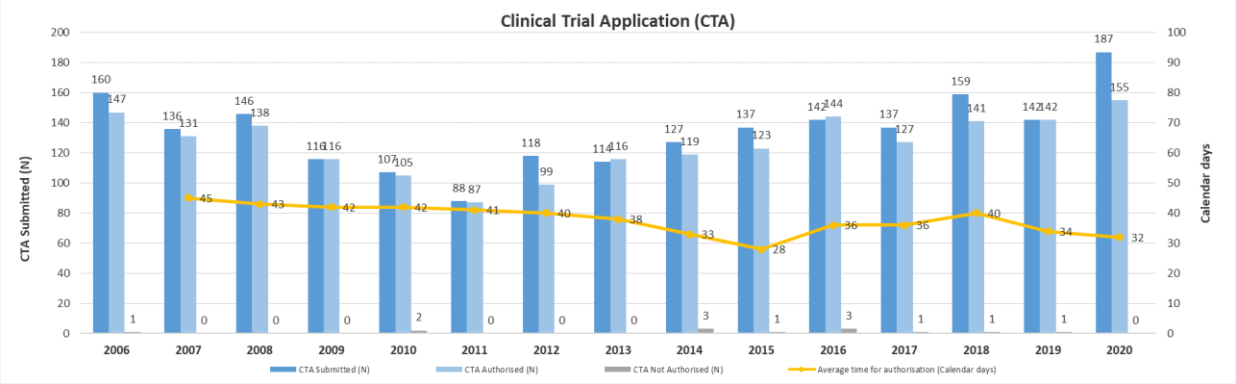

Figure 10 *Evolution of the number of clinical trials submitted and authorized (total number) in Portugal (from https://www.infarmed.pt/web/infarmed-en/human-medicines/statistics-of-clinical-trials-assessed-by-infarmed).*

This fact is of the highest importance since Portugal, compared with other European countries of similar size, has the lowest number of recruited participants and CTs/M. Table 11 shows results corresponding to submitted interventional studies both investigator and industry initiated. The following data were collected from 2016, except for Portugal, Sweden, and the Netherlands whose data was reported one year later. Despite having approximately half of the Portuguese population, Denmark has three times the number of CTs/M. Although Portugal has seen a positive evolution in CTs this last decade, showing significant potential for growth, implementation of effective and timely strategies may be pivotal to improve national results[9].

Table 11 *Comparison of Portugal with other European countries. Adapted from https://www.apifarma.pt/publicacoes/siteestudos/Documents/PwC_APIFARMA_Relatorio_Ensaios_Clinicos_Fev2019.pdf*

Country	CTs/M	Total CTs	Population (M)
Denmark	49.9	286	5.7
Belgium	44.6	506	11.3
Netherlands	32.1	548	17.1
Sweden	30.6	310	10.1
Spain	18.5	860	46.4
United Kingdom	14.9	978	65.6
Portugal	13.3	137	10.3

The low investment in advertisement and poor literacy of the population in clinical research might hinder the success of recruitment. The complexity of the processes, namely time-consuming negotiation of contracts and strict regulations, are also factors that compromise CTs. Clinical research is still not seen as a national priority by sites ABs. In addition, there is little involvement of general practitioners in clinical research, which may lead to reduced participant referral. Lastly, there is a limited number of investigators and other site staff who are fully committed to clinical research since the activity is performed during the professional's free time. In face of these alarming observations, effective and streamlined strategies that focus on qualification and work capacity of multidisciplinary healthcare professionals combined with high-quality data and good participant-investigator relationship are crucial to overcome recurrent barriers and subsequently, contributing to further CT development in Portugal[9,14].

2. Influential factors in the allocation of clinical trials by the pharmaceutical industry

Sites are responsible for the patient interfacing part of a clinical trial, directly impacting participant recruitment and engagement, the number and rate at which patients are screened, enrolled, and retained in a clinical trial. Therefore, the selection of sites is a process of great focus to pharmaceutical companies. The historical record has proven to be a strong predictor of a site's future performance. However, pharmaceutical companies rely solely on data assembled from their own trials, which may represent a limiting factor for a robust assessment[15].

During the complex process of clinical trial allocation, the decision of multinational pharmaceutical companies is determined by multiple key performance indicators (KPI). Patient recruitment, quality, costs, set-up at the trial, site commitment and experience are site-related qualities considered during site selection.

〉 Patient Recruitment

Patient population availability and timely patient recruitment represent some of the emphasized decision makers during site selection. A valid estimation of the

expected number of participants recruited is highly valued, as this factor is usually crucial to a successful recruitment, corresponding to a company's priority. This estimation usually is made based on recruitment and retention track record. How quickly a study can begin includes contractual procedures, and time from SIV to FPFV. A rapid start up time means a larger available period for enrolment, therefore increasing the chance to achieve the committed target (number of promised participants).

〉 **Quality**

Quality of data collection procedures, security and storage facilities are considered indispensable factors. Companies state that they rather choose high quality data over a high number of recruited participants. Quality is addressed when close monitoring takes place and support is given to sites in case of findings at prior audits or inspections.

〉 **Costs**

Even though being considered a secondary factor, a rise in costs could lead to the allocation of fewer clinical trials to the country. Industries control costs with grand plans and usually, the site price must be within acceptable ranges from the point of view of compliance.

〉 **Set-up at the site**

A site facilities evaluation is made according to the concurrent workload at the site, the number of employees, back up at the site, competing trials, site feasibility, and internal cooperation with other departments and the hospital management. Communicate with actively involved study stakeholders, as study coordinators or nurses, is considered crucial to address the resources available and site feasibility. This approach confirms the availability of employee-related facilities throughout the study lifespan.

〉 **Site personnel's attitude toward running a clinical trial**

The interest and commitment among site personnel is mentioned to be pivotal for a trial to succeed. Site personnel shall accept the trial in order to invite patients to participate. The right mindset also impacts the study recruitment. Hence, study members shall understand what participation in a clinical trial means, not neglect documentation requirements, and recognize this process as time-consuming.

〉 **Experience**

Even though being considered not imperative, site personnel experience in conducting trials is highly valued. Lack of experience is not seen as an exclusion factor, as companies want to expand research and access to the patients. After selection, companies try to meet the site needs, allocating more resources to training and monitoring at sites. Participation in prior phases of the current clinical trial and knowledge within the therapeutic field are considered important factors in early phase trials, as these include several procedures that need to be completed within a narrow time limit.

Recruitment-related factors and data quality are among the most important factors to multinational pharmaceutical companies during trial allocation, whereas costs seem less important. Furthermore, the right mindset and site engagement is considered imperative, in contrast to the experience in conducting clinical trials. Multinational pharmaceutical companies focus on reaching enrolment goals quickly, valuing patient population availability, timely patient recruitment and start-up time. Moreover, companies have a low impact on recruitment, depending on sites recruitment skills once the trial starts a run-in period[16].

2.1. Country and Site Selection

The global team provides information related to a new clinical trial. The CSM, medical advisor, and TA Head evaluate the interest and feasibility of potential sites, at a national level. After confirming local participation, the local team must answer a questionnaire to demonstrate country interest and possibility of developing the trial then the global team evaluates each country proposal. When approving the country participation, the global team defines the number of

participating sites as well as country commitment. The next figure outlines the process of country and site selection in a new clinical study, sponsored by Novartis (figure 11).

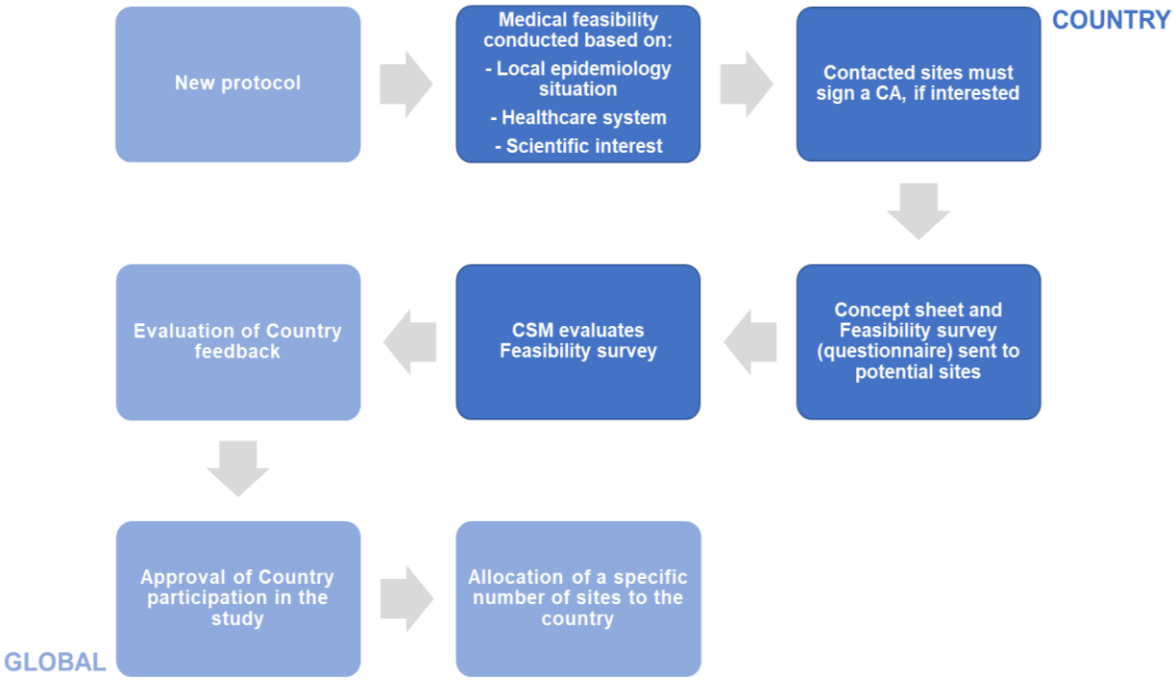

Figure 11 *Process of feasibility evaluation and national site selection.*

In Portugal, the key factors considered during site selection are the potential number of eligible participants and the operational potential. The latter is composed by 9 scoring parameters, presented in table 12. Each site is scored according to the level of performance for each indicator, whose overall performance is translated using a site segmentation tool. In like manner, site selection is based on the combination of the previous score with the number of site planned participants.

In competitive studies, the number of site active protocols and trials allocated per SC are indicators considered during site selection.

It should be noted that the evaluation among sites is based on the previous site participation for similar types of study protocol, if possible, or studies with similar pathologies, as the design of the protocol itself can affect site performance.

Table 12 *Scoring parameters of operational potential.*

Indicators of Operational Potential

• Number of competitive studies in specific indication
• Study Staff available
  - Shared resources, dedicated resources, Clinical Research Unit
• Clinical Team Available (medical/nurse)
• Past Recruitment Commitment vs Actual Trial Recruitment
• Historical Information on involvement/experience in clinical science
• Historic quality of data captured and time to response to query
• Involved in Novartis strategic activities
  - Investigators influence in TA
• SIV to FPFV
• Approval Timelines
  - Time from submission to hospital to approval by administration

3. Risk Based Approach

The pharmaceutical industry was heavily relying on On-site monitoring approaches, focusing on full SDV to guarantee subject safety and data quality. SDV is the process to confirm the accuracy of data transcription, by comparing the data collecting system to the original source of information. Even though this approach is quick at identifying issues and prevent them from recurring, it also has a negligible effect on data quality as it only helps to detect the same type of deficiency, not guarantying the identification of all subject safety, focusing more on specific situations instead of processes. Therefore, the low return has driven industry to transition to Risk-based Monitoring (RBM). RBM is a process used to see beyond the source data, to define upfront what and which are the critical data points that require focus and in parallel holistically understand the critical processes from each site to mitigate risks, so they do not become major audit and inspection findings.

SDR is based on 3 principles:

1. **Review of Quality of Documentation**

The CRA checks source quality and compliance, relying on a set of principles named ALCOA^{+}. After reviewing the source for ALCOA^{+} compliance, SDV is performed to specific critical points to ensure the eCRF data points match the source. For example, when it comes to confirming data completeness, the existence of newer information must be verified.

2. **SDR for protocol compliance**

Source data should be reviewed to fully detect both important and non-important PDs, focusing on data that is not captured in any other database.

3. **Review of site process**

The CRA assesses the processes holistically, which entails looking at source data and systems as a whole and not just as a sum of their parts. Novartis has an application that contains key clinical trial data. The application combines key performance and risk data from a variety of sources. For this, a changing color system (green, amber, and red) is used to translate the frequency of key risk indicators (KRI), enabling a better understanding of risks associated at the trial and site level. Therefore, the CRA approaches the site, considering the proportion of risks and asking the right questions to evaluate the critical processes. Monitoring critical processes is the shifting of mindset from data monitoring to process monitoring[17].

3.1. Case Scenario

A site that does not meet nor respect protocol requirements, SOPs, guidelines, GCPs, or ALCOA+ principles, will certainly challenge monitoring. The CRA facing this situation initially focused its energy on finding a strategy that could make the site see what they needed to change to meet the study requirements. However, and even trying constantly new approaches, the lack of site responsiveness and

collaboration drained all the energy from the CRA. In this case, the CRA was “feeling” the site’s responsibility as her own. After adopting the RBM approach, the CRA shifted the mindset: rather than investing the time on how to improve the way the site was seen, the CRA started supporting them to be compliant. The site needs to be in full charge of their source and CRF documentation. The study members must know what their roles entail and be alert and make every effort to meet the protocol requirements.

Instead of focusing on data points only, the CRA decreased SDV and SDR, adopting a process-driven monitoring approach, by addressing the most relevant errors related to subject safety, data integrity, and or regulatory compliance.

4. Site Card

There has been enormous interest and investment, driven by the soaring costs and declining of drug productivity, in tools and technologies able to improve and optimize the efficiency of clinical trials. The number and quality of sites involved are crucial value-drivers, as they impact cost-per-patient, time-to-market, and the societal benefit of bringing innovative therapies to patients in need.

Multi-site clinical trials have driven significant changes in medical practice, and compared to single clinical trials, offer larger and potentially more representative samples. Active site engagement is a key factor in large multi-site clinical trials as variability in the performance of trial operations across sites, with different personnel and clinical practices, may impact not only participant recruitment and retention but also scientific integrity[18].

Tracking a site's operational performance enables the sponsor to identify ways to continuously improve processes for future studies. Sponsors are increasingly using KPIs and KRIs to compare the operational performance among sites and demand higher levels of metrics-driven performance.

KPIs aim to:

- Assess the status of the trial
- Identify corrections that ought to be made
- Suggest a course of action
- Measure the results[19]

KRIs are used to monitor identified risk exposures over time and aim to:

- Indicate the level of risk related to each activity
- Provide early warning on potential events that may disrupt the project[20]

KPIs measure how well an activity is being performed, while KRIs measure the possibility of future adverse impact.

The TMO team assigned the intern the construction of a site card. The site card retrospective approach translates the performance of contributors, by acknowledging them with information that can be used for future trials or for

process improvement efforts. The aim of the project was to define the performance indicators and assemble them in a template applicable to a broad range of studies to be later presented either at the end of the study or at the beginning of a new study, aiming to remind the site of previous study performance.

4.1. Selection of performance metrics

Despite defining the KPIs and KRIs, the site card is an adaptable document that is built according to different factors. Hence, the site card gathers the following metrics:

〉 **Timelines**

After SIV, the site can start recruiting and the FPFV corresponds to the first subject screened, and with this achievement, the site becomes active for the trial. Therefore, the site card presents both site event dates and the first events that took place at the national and global levels. By displaying 3 levels of events (site, national and global) for both metrics, the site can position itself, by measuring the time that took to achieve the milestones.

〉 **Recruitment Summary**

Planned participants that entered treatment versus actual participants show if sites are successfully meeting recruitment targets.
The recruitment rate is calculated as follows: actual participants to enter treatment/ planned participants to enter treatment. Achieving the site commitment means obtaining a 100% recruitment rate. Thus, exceeding the planned number of included participants is translated into a recruitment rate greater than 100%.
SCR failures are defined as potential subjects who undergo screening but are not enrolled in a clinical trial, because at least one study criterium was not met. Therefore, the SCR failure rate is calculated as follows: number of participants who dropped SCR/ number of participants who entered SCR.

〉 **Site Cycle Time Analysis**

Once a site is selected, both site and sponsor work to complete study start-up activities to quickly activate the site. During the start-up period, activities such as collecting site regulatory documents for IRB approval and managing financial agreements must be performed to initiate the site and activate the recruitment. Thus, SSV to SIV and SIV to FPFV are presented in the site card, showing how long it takes a site to start-up and activate the recruitment and treatment period, respectively.

Concerning the FA, 2 metrics were considered: the time (days) between the date when the first draft is sent to the site and the date that the sponsor receives an answer; and the time (days) between the date when the final version is sent to the site and the date of approval (fully signed FA received by sponsor). Long cycle times may signal the site to identify root causes delaying the process. Short cycle times may translate sites' responsiveness.

Ethics approval is one of the first milestones in the life cycle of a clinical trial[21]. Despite recognizing the importance of this metric, it was decided not to include it in the site card, as it involves an external stakeholder and consequently does not translate an only-site performance.

〉 Data Quality and management

Queries within EDC systems, much like protocol deviations, are also consistently unavoidable due to human error. Queries are generated when eCRF does not match the corresponding source documents and or an explanation is requested through data review[22]. Commonly, queries are caused either by documentation's incompleteness, namely missing medical history information, evaluation/parameters, or pages, or are raised by data management team after medically reviewing participants data. Thus, sites ideally should take up to 7 days (average) to solve queries in EDC.

Site is expected to enter subject visit data in eCRF within 0-5 days with a maximum of 20 calendar days after the event date. Sites with a persistent delay (superior to 21 days) should be closely monitored as it may impact the completion of the trial on time. Data entry must be done as quickly as possible and simultaneously maintaining data quality, otherwise, the query rate may increase.

A protocol deviation is generally an unplanned excursion from the trial design or procedure defined in the IRB approved effective protocol version. PDs can be split into important and non-important. Important PDs may significantly impact the completeness, accuracy, and/or reliability of study data or participant's rights, safety, and well-being. Thus, most of important PDs will fall into one of the following categories:

- Participants who entered the study despite criteria not being met
- Participants who should be withdrawn from the study but remained
- Participants receiving the wrong treatment or incorrect dose
- Participants receiving an excluded concomitant treatment

Other departures from protocol not falling into one of the categories mentioned previously, are mostly considered non-important PDs[23]. Thus, PD rate is calculated as follows: total number of confirmed PDs (non-important and important)/ total number of treated participants.

Issues are defined by events in the conduct of the clinical trial at the site or an inadequate process that may lead to deviations from the trial protocol, SOPs, GCP and/or applicable regulatory requirements. Issues are classified as critical and non-critical, regarding severity. Critical issues represent scientific misconduct and potentially impact participants safety, rights and/or well-being, data integrity, IMP quality or efficacy. Concerning non-critical issues, these have a moderate severity or potential to affect data quality and participants rights, safety and/or well-being, if left unresolved. Therefore, the site card displays the total number of critical and non-critical issues.

4.2. Data and Sites Performance Assessment

For this project, 6 CTs (A, B, C, D, E, F) from different TAs in the final phase were evaluated. Data assessment will be done per metric, as the same metric may differ for different studies.

4.2.1. Recruitment Summary

Study A aimed to determine superiority in reducing heart failure events. In Portugal, there is an emergency service that assists patients experiencing a stroke or myocardial infarction. This service consists of a network of institutions prepared with the necessary facilities (operating rooms) to quickly assist patients.

Sites A1, A3, and A4 are considered leading institutions in the cardiology field, having achieved a 133%, 167%, and 180% recruitment rate, respectively (figure 12).

Concerning site A2, this did not have a cardiac catheterization laboratory, as it was a requested facility for the study conduct. Thus, when facing severe strokes, the site referred participants to another institution with the necessary equipment. However, as requested per protocol, participants should be included 7 days after experiencing infarction or strokes symptoms. In this case, participants were treated in the equipped institution and after returning to the previous institution, were excluded from the study, as in most of the cases, the 7-day deadline had been exceeded. For these reasons, the site's commitment has not been met.

Site A6 was in a similar position, as it also needed to refer participants to another institution. However, contrasting to the A2 site's performance, site A6 achieved a 180% recruitment rate. This may be since participants returned to the first institution before having experienced the symptoms in less than a week and the study team had a proactive approach directly impacting recruitment.

Regarding site A5, this had the lowest recruitment commitment, as the division of the site was considered. Participants were referred to the site's division with the required equipment and facilities to conduct the trial, however, it had a lower pool of participants. Despite having had a more conservative and realistic approach, the site succeeded by achieving a 167% recruitment rate.

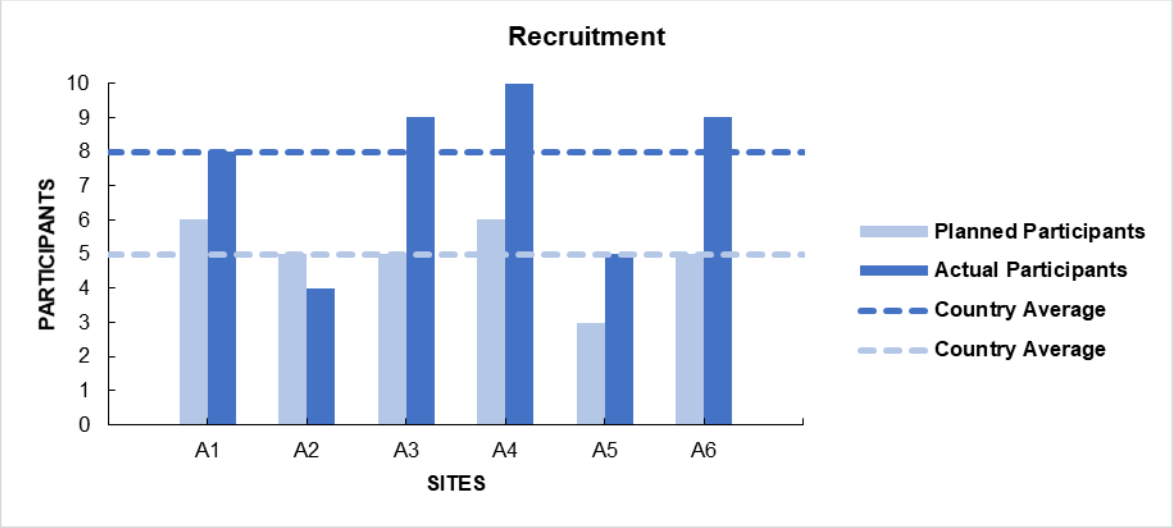

Figure 12 *Planned Participants vs Actual Participants per site and respective country averages for study A.*

Regarding study B, figure 13 shows a higher planned participants' country average comparing to the actual participants' country average, deferring in 1 participant. The sites (B1, B2, and B6) that had a more conservative approach, regarding the number of planned participants, exceeded their own commitment, reaching a higher number of recruited participants. The remaining sites (B3, B4, and B5) adopted a more ambitious approach and ended up not achieving the commitment.
It is clear the impact of the site B3 performance on both country averages, as this site committed to recruit 3 participants and finished up not including any. This double-blind study had a heavy workload for both the study team and participants. The only participant that entered screening resigned from the ICF, realizing later the required bi-monthly visits at the site since participants could not perform IMP self-administration. Following this SCR failure, the site reported the site inability to recruit due to the unavailability of participants. Hence, this result may compromise the selection of the site for future participation in a similar TA study. The SCR failures of the site B4 were mostly due to not meeting one of the inclusion criteria.

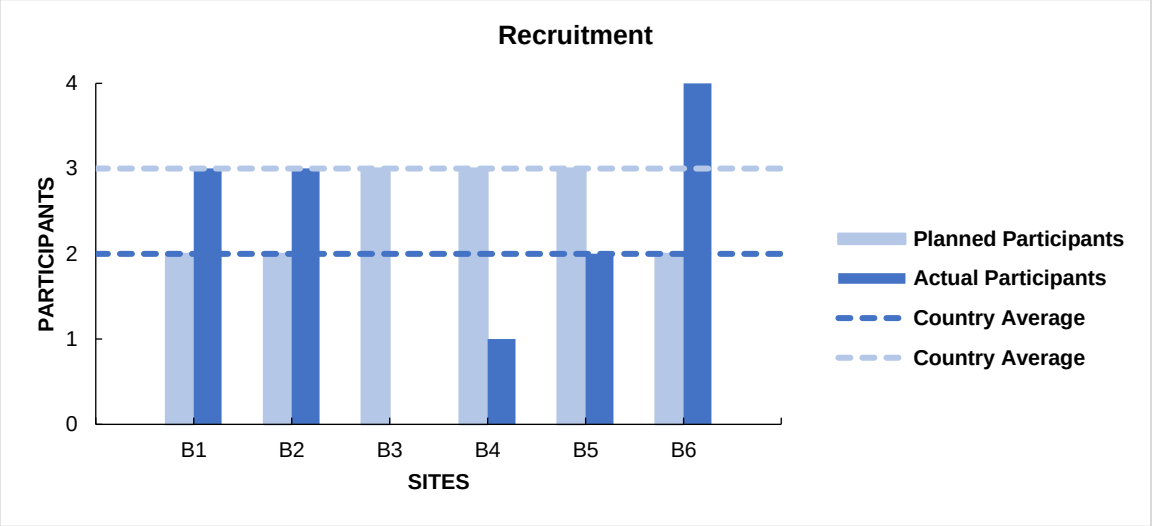

Figure 13 *Planned Participants vs Actual Participants per site and respective country averages for study B.*

Site C3, from previous study participations, is known to have a great relationship with Novartis and traditionally exceed the expected in terms of recruitment (figure 14). Being this a rheumatology trial and the site is mostly focused on rheumatic diseases, the pool of participants is higher, and the commitment could be easily achieved (recruitment rate of 167%).

C4, with the lowest recruitment rate (50%), is a small site, and at the time of the study the PI worked for a long period alone not being motivated to recruit, being this mostly caused by the lack of support. Nowadays, and after including other study members, a greater performance is noticeable in the site's recent studies participations.

Despite having reached a 100% recruitment rate, these results do not translate the great potential of the site C5 to recruit, as seen from previous studies. Even though having a study team extremely motivated and actively involved, the participants dynamic is an external factor that may compromise the performance of the site and must be considered in this situation.

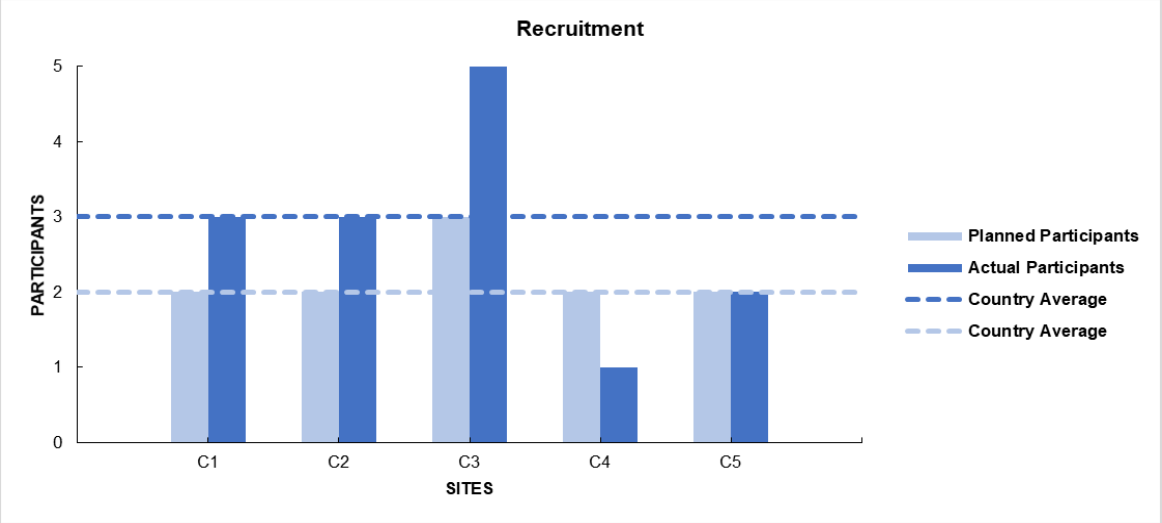

Figure 14 *Planned Participants vs Actual Participants per site and respective country averages for study C.*

The following oncology study shows 2 sites that are nationally recognized in the TA and have a high recruitment potential (figure 15). Even though having planned to recruit 3 participants, both sites exceeded these numbers, achieving 6 and 5 actual participants that entered the treatment.

Regarding site D1, it must be highlighted that it was considered a top recruiter at a global level. Despite having had shown to be willing to recruit more participants, the global team was unable to allow this request, as this site had achieved the maximum recruitment percentage. To avoid biased results, a limited contribution for each site is referred to by statistics. Thus, by imposing a limited percentage, the global team prevents bias to interfere with the quality of results and the outcome of the research.

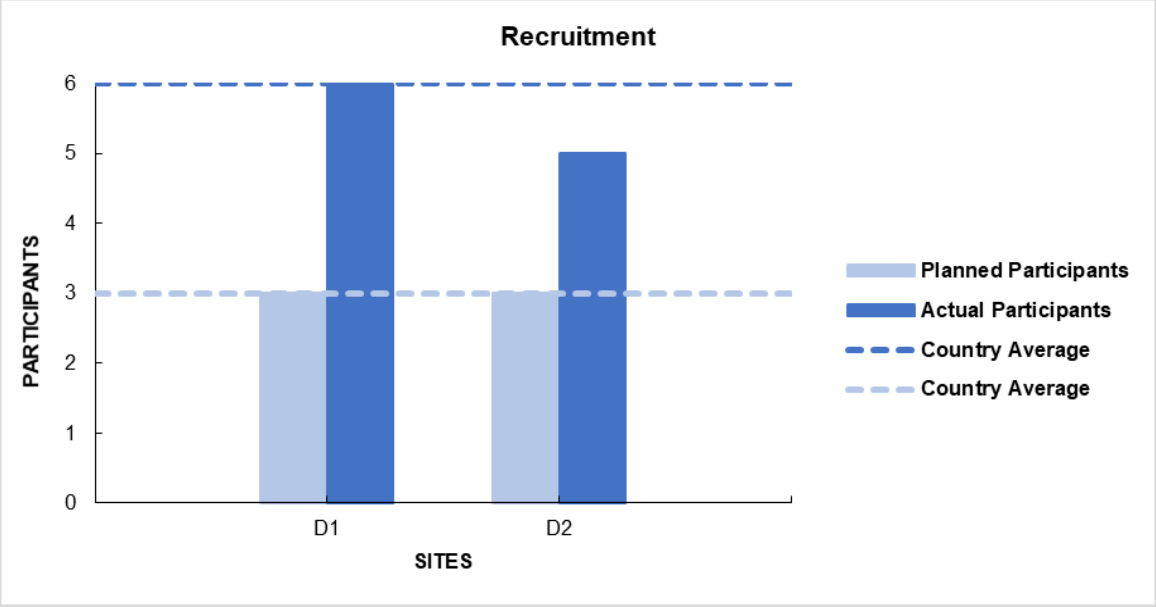

Figure 15 *Planned Participants vs Actual Participants per site and respective country averages for study D.*

Site E3 stands out with a recruitment rate of 250%, as it has more than doubled (x2.5) the number of planned recruited participants (figure 16). This result may be justified by the high level of commitment from the PI, which highly contributed during recruitment. The PI not only knew well the study protocol but also accompanied the participants during their visits.

Site E1 performance contrasts with the one seen for site E3. Despite being highly motivated for clinical research and recognized in the TA, the PI may had not been able to motivate the remaining study team members. In addition to being extremely disorganized, this site has also a poor coordination capacity, which may be factors compromising the recruitment rate achieved (67%).

From past collaborations, site E5 is known to have a chronic coordination problem. The extreme workload disables the coordination team to provide the necessary support for each study. In this case, the participation of a key opinion leader (KOL) was also considered during site selection. KOLs have a high level of expertise and impact in the studied TA and frequently assume the role of national coordinator.

The major perk of site E4 is having a clinical research unit, with a team fully dedicated to clinical research that provide a great support to PIs. Hence, the noticeable positive performance, resulting in a recruitment rate of 150%.

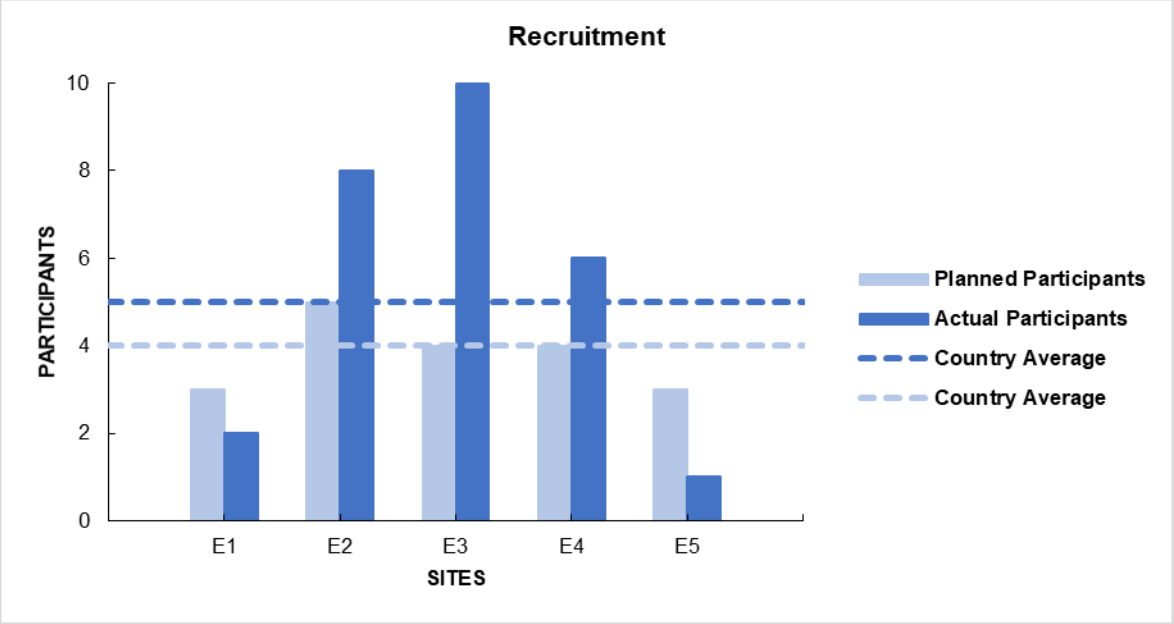

Figure 16 *Planned Participants vs Actual Participants per site and respective country averages for study E.*

Site F5 had one SCR failure and despite having committed to recruit 4 participants was unable to recruit any participants (figure 17). Site F1 had initially committed to recruit 5 participants, which was later readjusted to 8 participants. Flexibility and adjustments occur during the study to compensate sites that fail to achieve the promised objectives. However, the sum of the sites' commitment (43 planned participants), considering the initial 5 participants for site F1, is higher than the Novartis Portugal commitment agreed with the global team (40 planned participants). Therefore, the recruitment of 36 participants resulted in a 90% recruitment rate.

Site F5 translates a site selection based on the PI's impact, both in the TA and in his peers. The sponsor provides the IMP for the investigator, enabling an assessment prior to commercialization and to combat possible skepticism toward the IMP. The inclusion of a KOL is highly valued, as it can add considerable credibility to the CT.

The common aspects mentioned among sites were the fact that the IMP was not administered orally but by subcutaneous injection, and the comparator was not considered a first-line drug for multiple sclerosis. Multiple Sclerosis commonly affects older people, and generally, these prefer to take oral medication rather

than injections and have easier access to the pharmacy rather than the site. These factors may have compromised the results, resulting in some sites not achieving their own commitment.

Figure 17 *Planned Participants vs Actual Participants per site and respective country averages for study F.*

4.2.2. Site Cycle Time Analysis

Study A's recruitment period overlapped with a Novartis-sponsored competitive study (figure 18). Considering the participation of the same sites and study teams for both studies, the global team prioritized the competitive study, delaying study A’s recruitment period. The ongoing recruitment of the competitive study disabled sites to conduct SIVs and further include participants. Hence, the unsatisfactory results and country averages for study A shown in the following chart.

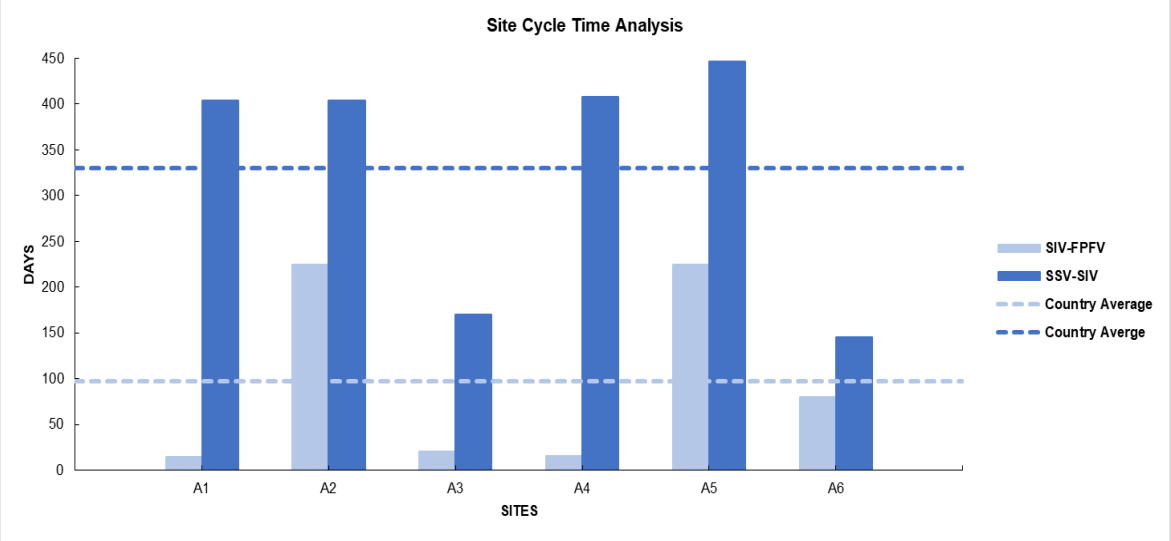

Figure 18 *SIV to FPFV vs SSV to SIV per site and respective country averages for study A.*

Concerning site C4, and as mentioned previously, the factors affecting the recruitment, firstly compromise site cycle time metrics (SSV-SIV and SIV-FPFV) (figure 19).

Sites B and C were both rheumatology trials studying different rheumatic diseases. Study B started earlier than study C and considering the same type of requested documentation for the study approval, the whole process consequently was accelerated. For both studies, the same study teams were involved, thus site-sponsor relationships enabled processes, such as review and approval of FAs to be streamlined.

The reasons prior mentioned may explain the lowest SSV-SIV country average (200 days), which means the following sites were the fastest to become active.

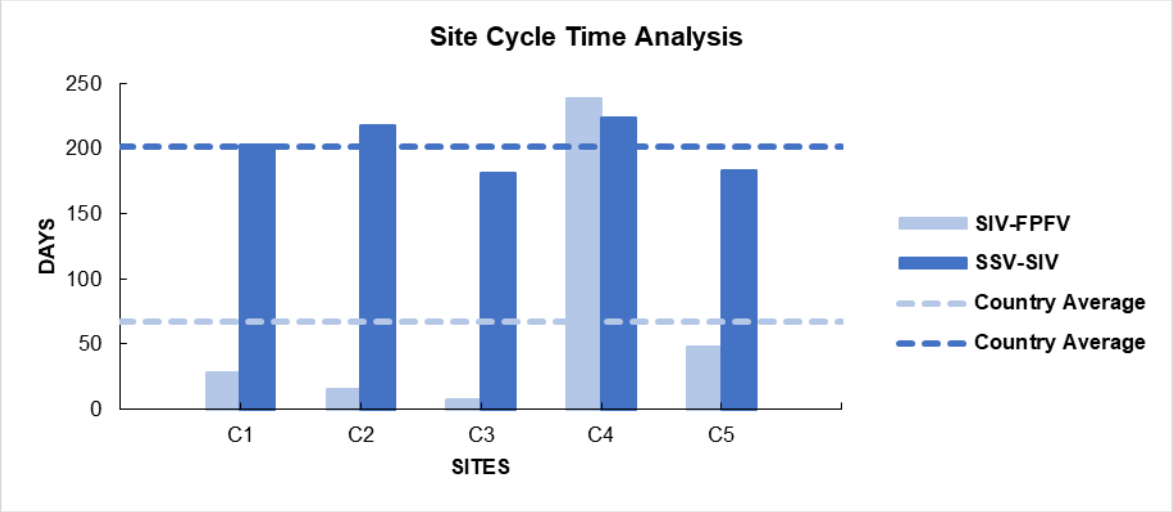

Figure 19 *SIV to FPFV vs SSV to SIV per site and respective country averages for study C.*

Oncology is a health field extremely dependent on time, thus when performing SIVs, many sites already have identified participants to rapidly start the treatment (figure 20). This is because either the participant undergoes immediate treatment or will have to opt for another treatment, in case the study has not been started yet.

A smaller sample impacts majorly the country average. However, both sites stand out since site D1 included the first screening on the same day of becoming activated (SIV) and site D2 took 11 days to include the 1st participant for screening. It took an average of 331 days for both sites to reach the milestone (SSV-SIV).

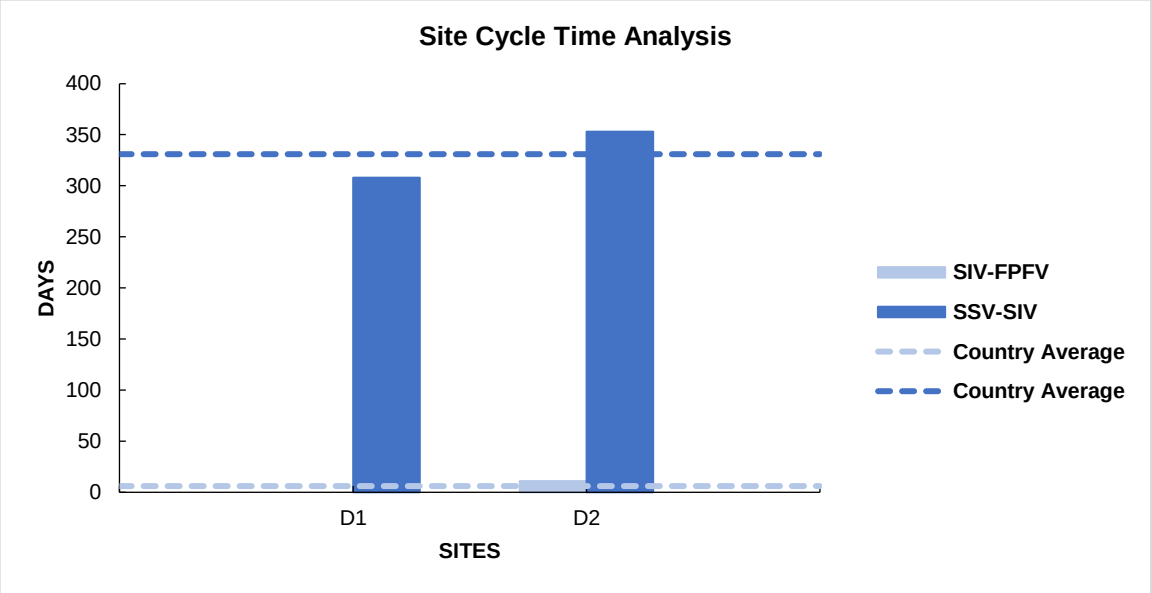

Figure 20 *SIV to FPFV vs SSV to SIV per site and respective country averages for study D.*

Authorities request identical studies (same protocol) as they are conducted with different study teams, participants, and data collection systems to avoid bias. Study F was one of the identical parallel clinical studies submitted (figure 21). The simultaneous submission to CEIC resulted in the failure of one of the studies. Facing this situation, the national team requested the global team to transfer the allocated sites from the disapproved study to the approved one. After receiving positive feedback from the global team, rather than submitting an initial submission, a substantial amendment was submitted to CEIC. Authorities have 60 days to approve an initial study submission, whereas an amendment takes 30 days. Sites F6 to F11 were allocated to the rejected study and later reattached to the identical approved study. For this reason, it is noticeable a shorter activation period (SSV to SIV) for these sites compared to the other ones.

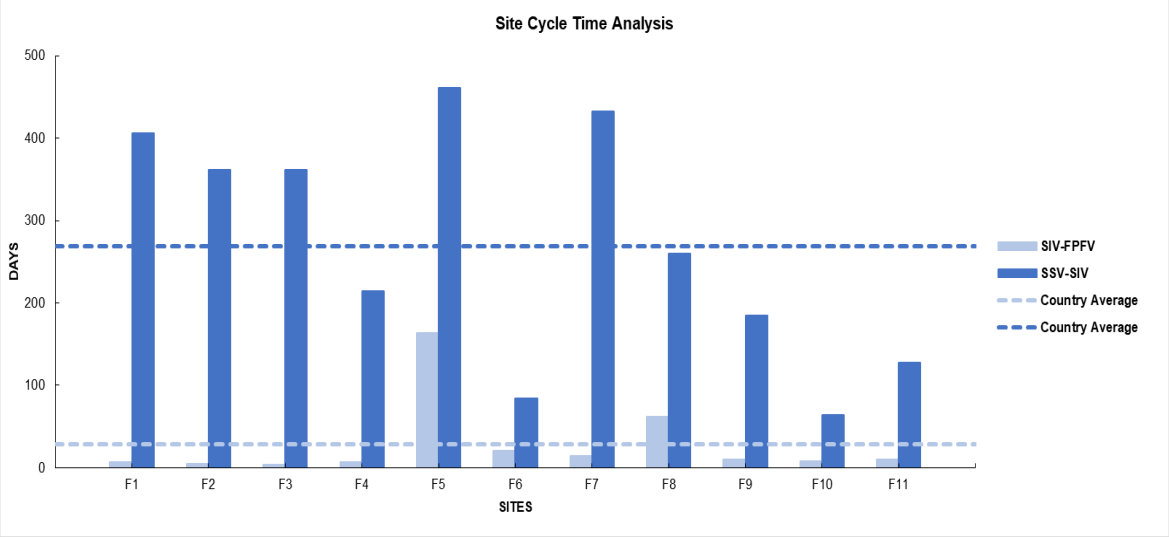

Figure 21 *SIV to FPFV vs SSV to SIV per site and respective country averages for study F.*

CEIC's performance, review and approval of FAs, and pace of documents collection to initiate the site are factors that directly impact the SSV-SIV metric. CEIC experts have 15 days for the evaluation of new trials, and when there are no remaining questions, the process proceeds to discussion and voting at the plenary session, which takes place every 3 weeks. Hence, the sponsor tries to submit the study for authorization close to one of the planned plenary sessions to lose no time.

It is possible to see a similar pattern in the charts, showing that sites take longer to activate the site (SSV-SIV) than to activate the recruitment (SIV-FPFV). Regarding the sample of studies presented, sites take from 202 to 430 days to become active (SSV to SIV), which means on average sites linger 6-7 months to more than a year to start recruitment.

4.2.3. Financial Agreement

Site A5 takes the longest to review and approve the FA (figure 22). The reason behind this performance may be the site's organizational complexity, as there is an extreme workload for the study personnel.

A longer time to review the FA draft may be also due to the frequency of questions raised by the site, which may need to be adjusted by the sponsor. There are some sites that even though discussing the FA draft do not go further, retaining the documents at the site until CEIC approval is released. Thus, the draft review metric may be less realistic in relation to the FA approval metric.

Sites A2, A3, A4, and A6 collaborate with the same CRO, meaning that the process is simplified as the contract specialist CTA contacts one person that further distributes the documents to the sites.

Site A6 stands out positively, as it took 9 days to review and approve the FA, and this may be due to the later site submission and the collaboration with the same CRO working with sites A2, A3, A4 and A6. Consequently, the process becomes more streamlined, and the contract specialist CTA makes changes to the FA according to the suggestions applied to the previously submitted sites.

Site A2 accepts the process and approves before CEIC approval. After reviewing the FA draft, the final version is sent to the AB to be approved and signed. And this may be the factor behind the second shortest FA approval.

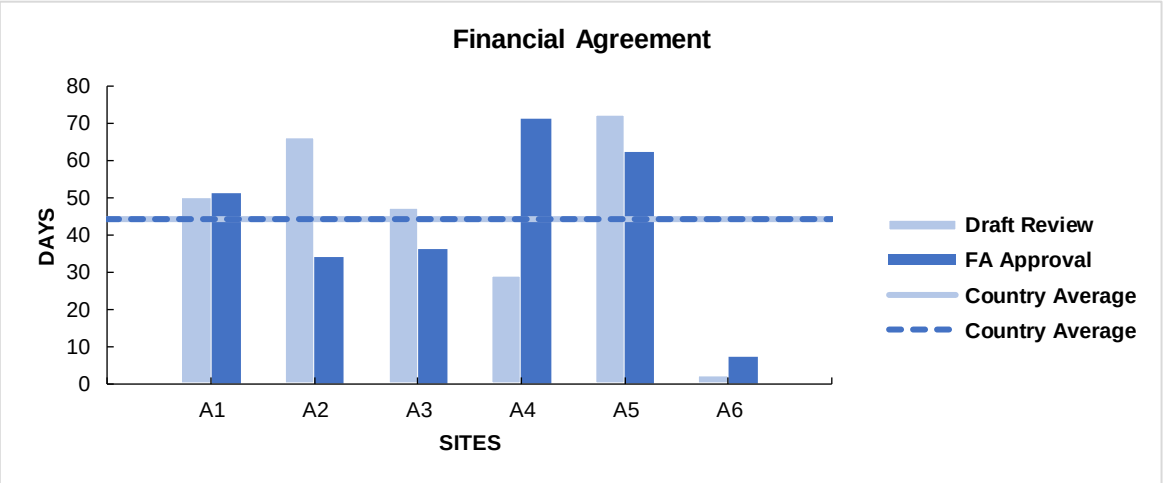

Figure 22 *Days for draft review vs FA approval per site and respective country averages for study A.*

Site B1 is a smaller site with a person responsible for the review and approval of FAs, working effectively, having taken a shorter time (27 days) to complete the process (figure 23). Regarding site B4, besides having an effective clinical research unit, the CTA financial specialist has a close relationship with the site and the responsible persons for the FA process.

According to previous data from past study participations, site B3 is known to take a long time to review the draft and approve the final FA version. However, as shown in the following chart, the site takes around 50 days for each metric, having an acceptable performance compared to other sites. This site may have been affected by a lighter workload, fewer FA alterations requested, a simpler protocol with fewer exams to perform, or a close follow-up from the CTA contract specialist.

Site B6 took 122 days to sign and send the final FA. At that time, after receiving the documents from the CRO, the AB used to keep the documents at the site, consequently delaying the sending of documents to the sponsor. Being this a metric dependent on the FA sending date to the sponsor, these actions/habits directly impact the assessment of the site performance. After discussing among peers and measuring the impact of the ineffective workflow, this site corrected their actions and nowadays has achieved a lower average of review and approval of FAs.

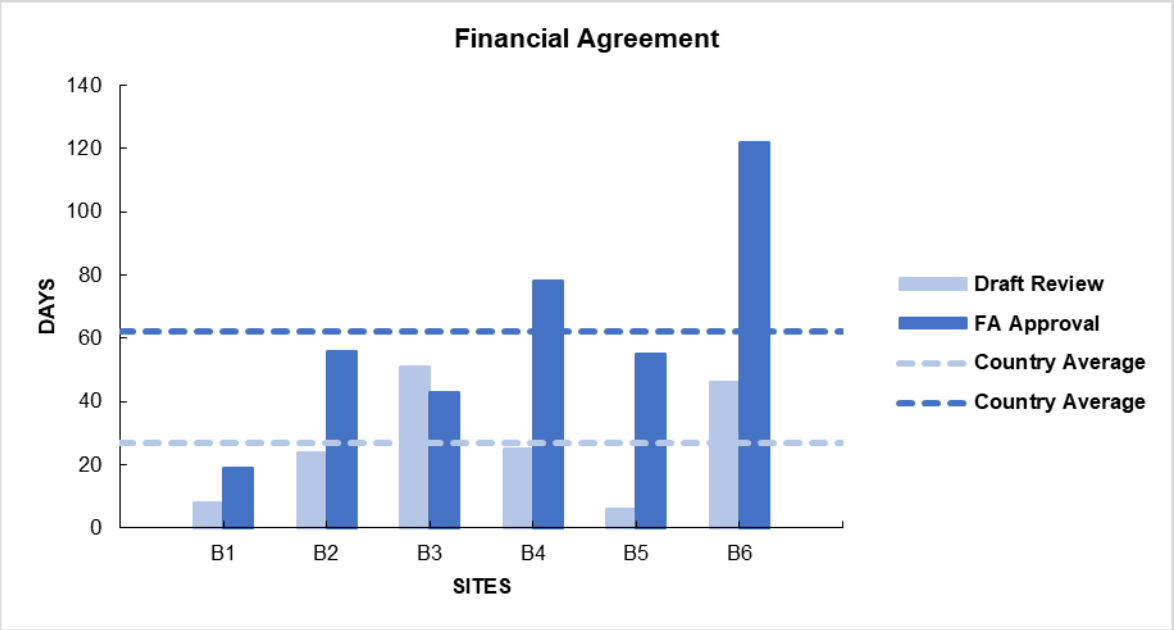

Figure 23 *Days for draft review vs FA approval per site and respective country averages for study B.*

Site F2 has a clinical research unit that works proactively (figure 24). For this study, the site closed the process effectively in 13 days. Regarding site F3, this collaborates with a CRO, and is likely the draft has not undergone any changes, as it was sent back to the sponsor on the same day.

Sites F6 and F10 belong to the same group and have a similar FA, taking practically the same time to complete the process.

Data show a huge difference between the review and approval of the FA for site F11, proving a superior efficiency of the AB when signing and approving the final version over the person responsible for the review.

Generally, the review of FAs may have been longer due to the complexity of the protocol.

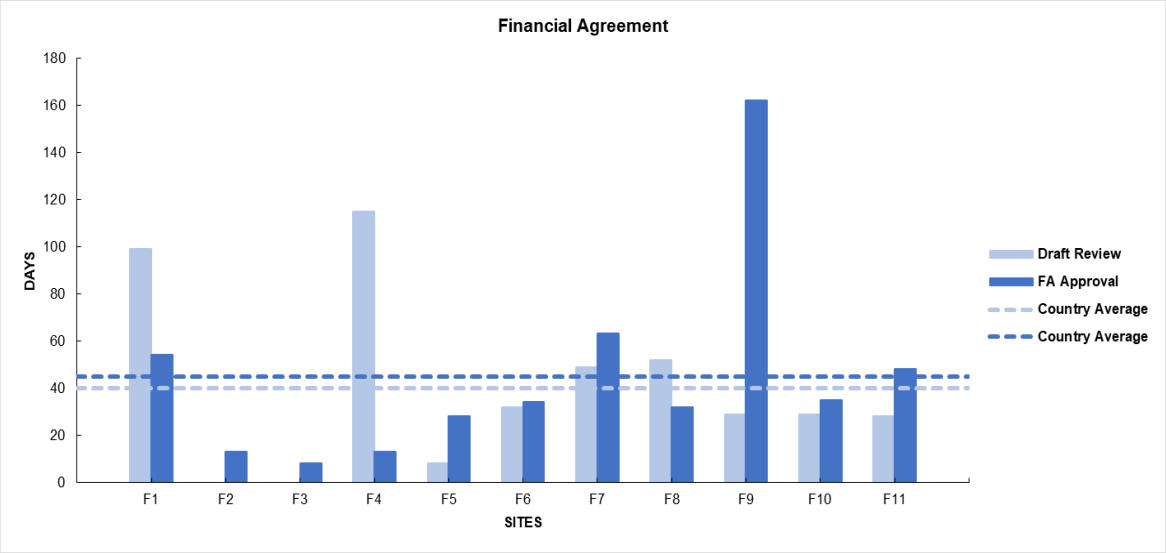

Figure 24 *Days for draft review vs FA approval per site and respective country averages for study F.*

4.2.4. Data Management

Data collection systems impact data management. Staff turnover, namely SCs have a direct impact on data management, as this stakeholder is in general terms, responsible for data entry and queries resolution. Study trainings and procedures ensure a level of standardization, good clinical practice, and data compliance, and address questions or concerns and avoid communication gaps that may appear during staff turnover[18]. However, study trainings do not always guarantee a

harmonized change and new members may not initially operate as efficiently as experienced members.

Novartis' systems collect data and evaluate sites' performance throughout the study's lifespan. A longer study is prone to greatly vary, and despite showing a possible improvement, outliers tend to compromise the averages of the metrics. Thus, it is not possible to capture a site’s performance profile solely from the averages of the metrics. It is crucial to dive deep into the site performance analysis by understanding tendencies over time and external influencing factors.

Sites presented in this report were all affected by the covid-19 pandemic. Consequently, several sites limited their access and compromised data quality. Sites able to continuously control and manage data had access to a remote data system. However, most sites proved to not be prepared concerning data collection systems when facing unexpected adversities. The denied access limited not only SCs’ activities, but also the CRA’s activities.

Regarding site C1, there was a high rate of staff turnover, namely SCs (figure 25). During lockdown, participants acceded the site to attend visits and SCs to prepare them. Thus, SCs were unable to perform data entry, resulting in long averages to enter subject visit data. Site C2 was closing data and participants were attending their last visits, being interrupted by the lockdown. Hence the long average for data entry. As for sites C3, C4 and C5, these likely no longer had participants at the time of the interruption. Site C4 was the only one to access the system remotely.

Queries resolution and the number of participants recruited are intrinsic concepts. C3 stands out as it recruited 5 participants, closing on average queries in 3 days. Of note, this site is considered high performing as typically enrolls a high number of participants and retains most of them through the completion of the study and is assisted by a well-structured and motivated study team. Sites C1 and C2 take longer to close queries, and despite recruiting the same number of participants (3), C1 shows a poorer performance for taking 3 more days to close queries. Sites C4 and C5 take 7 and 9 days to resolve queries, respectively. However, site C4 recruited 1 participant and C5 2 participants.

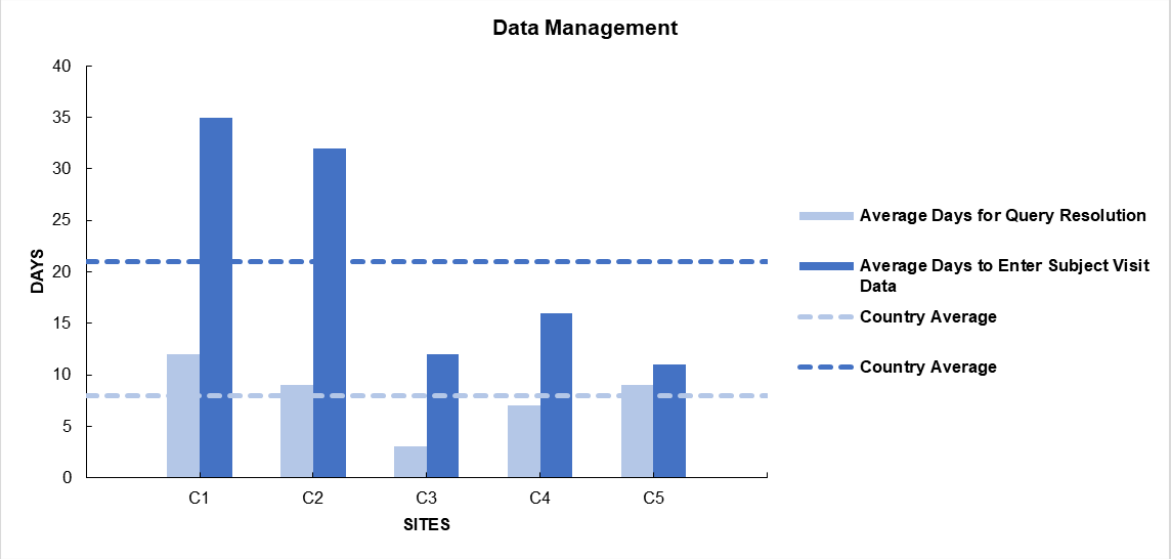

Figure 25 *Average days for query resolution vs subject visit data entry per site and respective country averages for study C.*

Data analysis must be deeply performed, as several external factors that determine data quality shall be considered. Interim analyses are performed before the completion of data collection and frequently lead to a rise of queries. Since queries are opened per participant, a higher number of participants frequently results in a higher number of queries.

There are no doubts, regarding the data dominance of sites with access to remote systems. The covid-19 pandemic has proved that most national sites are not prepared to face unexpected situations and take control over their own data. Very few sites have been left untouched by the covid-19 pandemic, therefore a deeper data analysis shall be performed to understand its impact.

All studies show a similar pattern: query resolution is performed faster than data entry. Queries notifications work as a traffic light and when interacting with this tool, CRAs get more alerted. Missing pages are notified differently, since CRAs are either informed by the global team or search for direct answers by running a report. By acceding the CRF, the CRA is not notified for missing pages. Therefore, data entry depends on the frequency of shared information by the global team and the level of awareness and alertness of the CSM to guide CRAs. Overall, close monitoring is the key factor to be in control over data entry.

4.2.5. Data Quality

4.2.5.1. Issues

The site card also includes the number of critical and non-critical issues for each site, as well as national averages. This metric translates the performances of both site and the CRA. Even though being guided by Novartis' guidelines, each CRA has its own standards and face situations differently. Thus, the assessment of processes performed by different CRAs will naturally lead to a variety of classifications.

Not only have guidelines changed over time but also the mindset of CRAs has shifted as well, as opening an issue was highly valued and nowadays, CRAs have a more cautious approach since from past experiences some issues were open and remained unresolved. When opening an issue, CRAs need to take time to identify the root causes and implement an action plan for each identified root cause and that can be for both the site and the CRA, in order to mitigate recurring issues. Therefore, the assessment relies on how a CRA opens and solves an issue.

This metric is extremely variable as it is affected by the CRA, type of study and sponsor’s standards, and guidelines.

4.2.5.2. Protocol Deviations

The rate of protocol deviations is influenced by the number of included participants, the site’s performance, and the study design.

Study B is presented to illustrate the impact that the study design may have on the PDs rate (figure 26). Site B3 is not included in the chart, since had a null inclusion of participants and this is a metric determined by this parameter. The design of this study defined an interruption of IMP for 30 days at the end of the study. The PI of site B2 disagreed with the protocol and considered it unethical as it would likely lead to participants experiencing an exacerbation. Being this a double-blind study, unhiding participants is an excursion from the protocol requirements, being consequently considered a protocol deviation. Site B2 has the highest PD rate as the PI unhid all included participants (3), resulting in a higher number of PDs and

PD rate. Concerning the remaining sites, Novartis informed these about the impact of unhiding participants on data quality, preventing the rise of the PD rate.

Overall, both average rates are satisfactory, being the global rate slightly below the national rate.

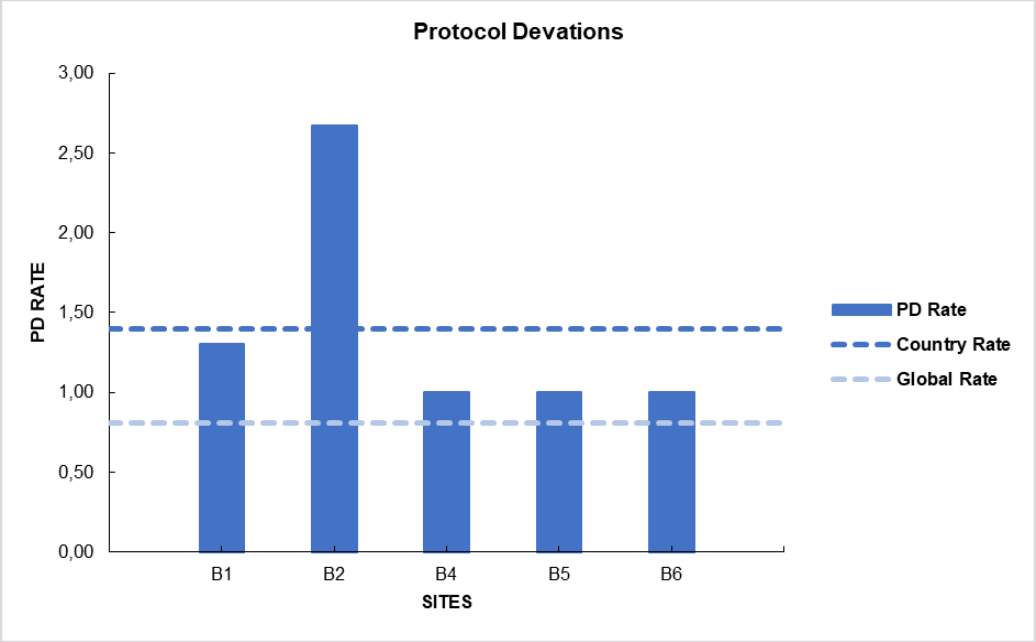

Figure 26 *Protocol Deviation Rate per site and respective country rate vs global rate for study B.*

5. Risk Management

Risk management is an important preventive practice that helps to identify, evaluate, track, and mitigate the risks that inevitably arise over the life cycle of an operating environment. The risk matrix is a tool often used to balance the weight of severity and probability.

Risks are uncertain events that when occur can either create positive opportunities or have a negative effect on a project's goals.

Evaluation or ranking of risks is based on risk magnitude. The magnitude of risks is determined by the probability of an event occurring and its impact or outcome (severity), being both metrics ranked on a four-point scale. The risk assessment values are determined by multiplying the scores for the probability and severity values together (figure 27). A risk that may cause some inconvenience is rated as having the lowest probability. As for risks that can result in catastrophic loss are rated the highest and warrant a particular treatment.

Risk mitigation strategies are crucial to reduce threats to project objectives as well as enhancing the opportunities (table 13).

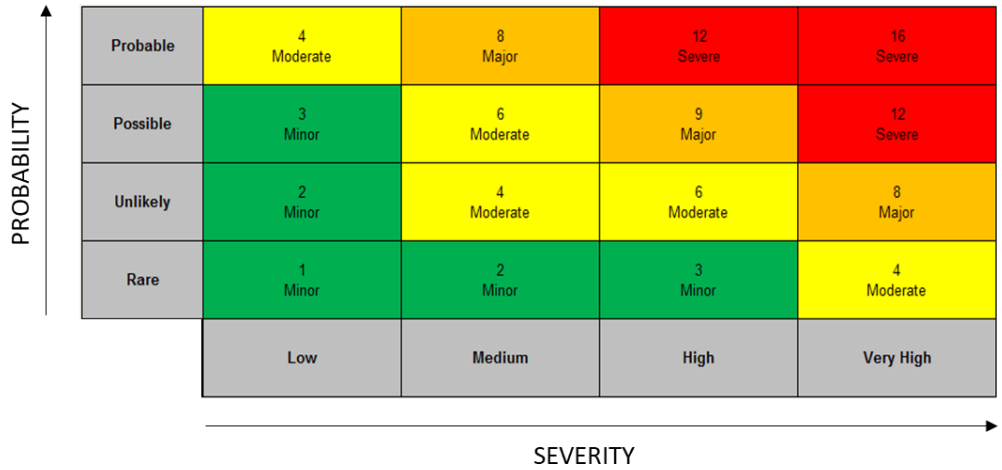

Figure 27 *Risk matrix 4 by 4 used to assess the risks involved in the internship.*

Table 13 *Identified risks in the internship, organized per category, and respective mitigations strategies. Classification of the positive or negative effect of each risk on the project, probability of occurrence, severity and total (risk assessment value).*

Category	Risk	Effect	Probability	Severity	Total	Risk mitigation strategies
Tasks Characteristics	Obtain an overview of tasks performed during the management of a clinical study in the context of the pharmaceutical industry.	Positive	4	-	-	Taking the initiative to perform different tasks and accompany different colleagues with different functions in the team.
	Do not fully comply with the proposed plan of activities for the internship.	Negative	2	3	6	Organize the internship period and assess, throughout the internship, the activities performed in order to ensure that during the remaining time the tasks not performed are reviewed and implemented.
Facilities	Inability to perform data assessments due to limited access to intern systems.	Negative	1	3	3	The institution ensures training and access to the intern to manage systems, whenever all required trainings are performed, and the access to the systems is requested per role.
	Inability to accompany CRAs during monitoring visits due to sites' opposition.	Negative	2	2	4	Host institution guarantees the prior notice and awaits authorization from the site or the research team for participation of

						an external element in the monitoring visit. Additionally, and aligned with the host's implementation of new work processes, participate in remote monitoring activities.
Communication/ interpersonal relationships	Regular contact with people with different backgrounds (personal and professional) and roles in the project.	Positive	4	-	-	Encourage communication and knowledge/experiences sharing with different colleagues.
	Poor communication among team.	Negative	1	4	4	Weekly team meetings promoting communication through sharing of experiences/knowledge.
	Poor adaptation to host institution	Negative	1	3	3	Greater involvement in ongoing projects and contact with different functions.
	Failure to transmit information concerning the execution of a task.	Negative	1	3	3	Clarify the most complex points of the task. Raise questions considering the availability of the colleagues.

6. Discussion

The increase of covid-19 cases and the general lockdown has rapidly challenged the pharmaceutical industry to implement remote monitoring activities. In order to reduce physical contacts, a shift in monitoring processes was applied, increasing the flexibility and inclusion of site staff, and enabling a more targeted review. Conducting short and frequent remote visits enables the sponsor to closely oversight the site, ensuring participant safety and data quality. However, remote assessments are only relevant if sites register data regularly. Despite the recognized advantages, remote monitoring activities can be seen as an increase of workload for SCs when preparing documents, increasing the responsibility of the study site. However, if implemented in alignment with risk base monitoring, as referred by both ICH-GCP guidance and HA, it will likely result in a more effective and efficient work. In Portugal, the current situation has shown that sites are not yet prepared to exclusively perform remote monitoring activities. Therefore, and recognizing the advantages of both off-site and on-site visits, the current situation could be an opportunity to revamp the traditional model by combining both visits to optimize the monitoring process.

Multi-site studies play a pivotal role in determining how medicine is practiced, by helping to drive reliable and generalizable knowledge on advancing medical treatments. Recruitment is a process of great interest to pharmaceutical companies since high-performing sites can not only increase the availability of data but also the probability of demonstrating statistically the studied therapeutic effect at the end of the trial. Recruitment may be determined by several factors such as: underlying operational quality, competitive studies, staff turnover, the misconception of available population, participants dynamic, and the design of the protocol. Site commitment has proved to be a crucial quality, as it may overcome several adversities that may appear throughout the study lifespan. Data has shown that despite facing the same adversities, motivation is a key factor for a site to succeed and data is not as affected as the ones that lack commitment and engagement.

The construction of a site card enabled the intern to deeply understand the variability in the performance of trial operations across sites, and the resulting

impact on participants recruitment, data compliance, and even internal validity of research findings. The site card aims on translating the operational quality of sites through KPIs and KRIs. This document assesses site performance realistically and should be embraced as a constructive criticism.

The document aims to acknowledge sites for best practices, achievements in recruitment, compliance, and notable milestones. Similar to Novartis' key performance and risk data systems, the site card uses the traffic light tool to show results. Results may be displayed in red if an improvement is needed, and in green, if the performance has been positive. In case sites achieve excellent results, such as taking up to 15 days to activate the site (SSV to SIV) the document includes a star next to the respective metric as positive reinforcement. National averages are also included enabling sites to have a glimpse of the bigger picture and position themselves in it. The site card delivery may take place either at the end of the study, to summarize sites' performance, or at the start of other studies to recall past results and behaviours and eventually motivate these to achieve better results.

Novartis is continuously working on improving systems to facilitate data management and improving operationality among sites. Currently, optimized systems and procedures have not yet been achieved so every effort is made by TMO to have all studies developed in Portugal achieving its goals. However, the key factor for the success of both sites and the sponsor is to follow a collaborative path toward constant evolution and improvement. The site card is seen as a document that will help both Novartis and Sites to learn and improve their performances for current and hopefully future trials.

7. Conclusion

Conducting a curricular internship during the second year of the master's degree was crucial to apply and reinforce the theoretical concepts taught in the first year.

The extraordinary circumstances surrounding the Covid-19 pandemic have forced the pharmaceutical industry to adapt to a new way of working, which also meant professionals have needed to rapidly evolve their skill sets.

Remote internships were highly encouraged by the current Covid-19 pandemic. Despite recognizing the advantages of physical proximity, a remote curricular internship has proved to be an enriching experience, having a tremendous impact on the intern. A half-year later of Novartis working at home enabled the intern to start the internship smoothly experiencing a dynamic environment. The team cooperation combined with communication and proactiveness were the key factors for the trainee's constant learning and improvement.

The proposed plan of activities included a wide range of tasks entailed to different TMO members. Therefore, it was possible to understand the role and the contribution of each member and overall, the organization of the TMO team.

Due to the limited access to sites a new monitoring system was adopted. During the training period the intern assisted remote visits and after reopening sites, accompanied CRAs in a few on-site visits. Having had the opportunity to experience a paradigm shift in monitoring was crucial to understand the advantages and disadvantages of both visits (remote and on-site) and the challenges the TMO team faced during the adaptation. Thus, the combination of both visits could be applied to optimize the monitoring process at the time remote procedures are well managed by sites.

There are no doubts regarding the central role played by sites in CTs, by directly impacting data quality, and consequently in medical practice. Establishing good relationships between sponsors and sites through CRAs has proved to be essential to manage the variability and improve operationality across sites.

The site card project enabled the intern to deeply analyze data and understand through results the performance of national sites. The assembled results translate the current state of clinical research in Portugal and the barriers that have yet to

be overcome. Overall, this tool may contribute to further CT development in Portugal.

The internship has without question enhanced not only the adaptability skills but also the communication skills of the intern. The improvement of information processing, job-specific technical skills/knowledge, and data analysis were the largest areas of development for the intern. These achievements led to requesting increased responsibility and asserting personal opinions. Teamwork was undoubtedly the key factor for the intern's soft-skill development.

The skills gained during this training period, have not only proved to be key, but will continue to serve the intern well in the future.

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