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MICAEL ANTÓNIO CARDOSO ALVES

RELATÓRIO DE ESTÁGIO CURRICULAR NUMA UNIDADE DE ENSAIOS CLÍNICOS ACADÉMICA – CRU²C

CURRICULAR INTERNSHIP REPORT AT AN ACADEMIC CLINICAL TRIALS UNIT – CRU²C

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Gestão da Investigação Clínica, realizado sob a orientação científica da Professora Doutora Ana Gabriela da Silva Cavaleiro Henriques, Professora Auxiliar do Departamento de Ciências Médicas da Universidade de Aveiro e sob coorientação do Professor Doutor Miguel de Sá e Sousa de Castelo Branco, Professor Catedrático da Faculdade de Medicina da Universidade de Coimbra.

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Muito obrigado a todos!

palavras-chave

dispositivos médicos, estimulação cerebral não-invasiva, investigação clínica, CRU^{2}C.

resumo

Este relatório descreve as atividades realizadas como estagiário na CRU^{2}C, a unidade de investigação clínica da Universidade de Coimbra, ancorada no Instituto de Ciências Nucleares Aplicadas à Saúde. O estágio realizado pretendeu colocar em prática os conhecimentos adquiridos durante a componente letiva do mestrado em gestão da investigação clínica.

O relatório de estágio inclui uma descrição do conhecimento adquirido e das atividades pré-estudo desempenhadas, nomeadamente no contexto de um ensaio clínico com radiofármaco, e em estudos clínicos com intervenção de dispositivos médicos. Inclui também dois casos de estudo relativos à investigação clínica com dispositivos não-invasivos de estimulação cerebral e às questões éticas e regulamentares associadas ao uso de dispositivos não-invasivos de estimulação cerebral.

Este estágio proporcionou a oportunidade de conhecer o trabalho que decorre numa unidade de estudos clínicos académica e de ganhar competências e experiência em investigação clínica.

keywords medical devices; non-invasive brain stimulation; clinical research; CRU^{2}C.

abstract

This report describes my experience as an intern at CRU^{2}C, the clinical research unit of the University of Coimbra, anchored in the Institute for Nuclear Sciences Applied to Health. The internship aimed to put into practice the knowledge acquired in the teaching component of the master's degree in Clinical Research Management.

The report includes a description of the acquired knowledge and the pre-study activities performed, namely in a clinical trial with a radiopharmaceutical, and in clinical studies with intervention of medical devices. It also includes two case studies regarding clinical research with non-invasive brain stimulation devices and the ethical and regulatory issues associated with the use of non-invasive brain stimulation devices.

This internship provided the opportunity to learn about the work developed in an academic clinical research unit and to gain skills and experience in clinical research.

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List of Abbreviations

AIMDD	Active Implantable Medical Devices Directive (90/385/EEC)
ASD	Autism Spectrum Disorder
aTBS	accelerated Theta-Burst Stimulation
CA	Competent Authority
CDM	Clinical Data Management
CEIC	National Ethics Committee for Clinical Research
CIBIT	Coimbra Institute for Biomedical Imaging and Translational Research
CIP	Clinical Investigation Plan
CNS	Central Nervous System
CPM	Clinical Project Manager
CPSP	Chronic Post-Stroke Pain
CRA	Clinical Research Associate
CRF	Case Report Form
CRU^2C	Clinical Research Unit University of Coimbra
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Application
CTD	Common Technical Document
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation (536/2014/EU)
CTU	Clinical Trial Unit
DIY	Do It Yourself
DLPFC	Dorsolateral Prefrontal Cortex
DTC	Direct-to-consumer
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EUDAMED	European Database for Medical Devices
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice
GNA	Grounds for Non-Acceptance
GPSD	General Product Safety Directive (2001/95/EC)
GSPR	General Safety and Performance Requirements
IAM	Identity and Access Management
ICD-11	International Classification of Diseases 11th Revision
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICNAS	Institute for Nuclear Sciences Applied to Health
IFU	Instructions for Use
IIT	Investigator Initiated Trials
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
INFARMED	National Authority of Medicines and Health Products, I.P.
iTBS	intermittent Theta-Burst Stimulation
IVDR	In Vitro Diagnostic Regulation (2017/746/EU)
MAH	Marketing Authorization Holder
MD	Medical Device
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive (93/42/EEC)
MDR	Medical Device Regulation (2017/745/EU)
MEDDEV	Medical Devices Documents
MSC	Member State Concerned
NB	Notified Body
NCA	National Competent Authority
NHS	National Health Service
NIBS	Non-Invasive Brain Stimulation
OJEU	Official Journal of the European Union
PIP	Paediatric Investigation Plan
PMCF	Post-Market Clinical Follow-up
PMS	Post-Marketing Surveillance
PND	Postnatal Depression
QMS	Quality Management System
RFI	Request for Information
RIA	Research and Innovation Actions
RNEC	National Registry for Clinical Studies
rTMS	repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SM	Substantial Modification
SMEs	Small and Medium Enterprises
SOPs	Standard Operating Procedures
tACS	transcranial Alternating Current Stimulation
tDCS	transcranial Direct-Current Stimulation
tES	transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
tRNS	transcranial Random-Noise Stimulation
UDI	Unique Device Identification
WADA	World Anti-Doping Agency

1. Introduction

During the second year of my master's degree in Clinical Research Management at the University of Aveiro, I had the opportunity to carry out a curricular internship at the CRU^{2}C, the clinical trials unit of the University of Coimbra, under the internal supervision of Professor Miguel Castelo-Branco, Professor at the University of Coimbra and Coordinator of the CRU^{2}C, and under the co-supervision (internship tutor) of Dr. Ana Pina Rodrigues, Researcher at the Coimbra Institute for Biomedical Imaging and Translational Research/ Institute for Nuclear Sciences Applied to Health (CIBIT/ICNAS) and Project Manager of the CRU^{2}C.

This curricular internship lasted for about seven months, a period that allowed me to acquire knowledge and experience in clinical trials and clinical studies of medical devices, and in the therapeutic areas of oncology and neuropsychiatry/neuroscience.

This internship report is the compilation of the activities performed at the CRU^{2}C.

The first part includes an introduction to the Clinical Research with Medical Devices, and includes the medical device definition, its classification, the changes introduced by the new regulation (Regulation no. 745/2017) and an overview on clinical studies of medical devices, including pre-market, post-market and other types of clinical investigations, strategies for planning and conducting successful clinical investigations, and the application process for a clinical investigation.

The second and third parts include two case studies, which summarize the theorical knowledge acquired while carrying out two of the activities proposed in the internship.

The second part comprises a case study on Non-Invasive Brain Stimulation Research in Chronic Pain, addressing non-invasive brain stimulation devices, aspects related to chronic pain, focusing on its definition, prevalence, and treatment options. It also includes the evidence on non-invasive brain stimulation and future research.

The third part is a case study on the Ethical and Regulatory Issues associated with the use of NIBS devices, covering the called do-it-yourself stimulation, the neuroenhancement and neurodoping practices and the marketing of these products and devices to vulnerable populations.

The fourth part describes the curricular internship, namely the vision of the host institution, the activities carried out during the internship and the deviations from the proposed initial activities plan.

In the Discussion section, a critical appraisal of the internship experiences is presented, including the challenges faced and if the objectives were met. The last section corresponds to the Conclusion, with an overview of the internship impact on my personal and professional growth.

2. Clinical Research with Medical Devices

2.1. Medical Device Definition

According to the Regulation (EU) 2017/745 (MDR), a medical device (MD) is “any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices” [1].

It should be noted that this definition excludes the devices with a non-medical intended purpose, such as equipment for liposuction. However, the Regulation contains the Annex XVI, which is specific to products without an intended medical purpose that must comply with the requirements of the medical device legislation. Furthermore, regarding the directives repealed by this Regulation (Directive 90/385/EEC [2], relating to active implantable medical devices and the Directive 93/42/EEC [3], concerning medical devices), this Regulation includes implants and reagents in the definition of a medical device. In medical purposes, it also includes prediction and prognosis and specific products for cleaning, disinfection, and sterilization of medical devices, which were considered accessories.

2.2. Medical Devices Classification

As in the Medical Devices Directive 93/42/EEC (MDD), the classification of medical devices in the MDR follows a risk-based system, with the aim of applying the appropriate conformity assessment procedure. Classification rules are based on the vulnerability of the human body, considering the potential risks associated with the devices (Article 51 and Annex VIII of the MDR) [1]. The device class is assessed considering the duration of contact with the human body (momentary, short-term, and long-term), the degree of invasiveness (invasive,

non-invasive), whether the device is active or not, and the part of the body affected by its use.

Medical devices can be classified in four main categories:

- Class I (low risk)
- Class IIa (medium risk)
- Class IIb (medium/high risk)
- Class III (high risk)

There is also a new subclass – Class Ir – which applies to reusable surgical instruments. Class I encompasses two other subclasses – Class Is (sterile) and Class Im (measuring function). The classification of the devices is addressed in Article 51 of the MDR [1], which directs to the 22 classification rules in Annex VIII of the MDR (that were 18 in the MDD). The additional rules address the integration of the classification of active implantable devices, breast implants and joint replacements. Additionally, these rules classify new medical devices that were not previously considered, such as devices with nanomaterials, intervertebral disc replacement implants, inhalers, and active devices that emit ionizing radiation for therapeutic purposes. Also, according to Rule 11 of the MDR, software can be classified as a medical device (SaMD) [1].

Although presenting more rules, the approach to classification described in the MDR does not differ substantially compared to the MDD. However, in the clarification process and the roles of the different stakeholders, the MDR is more thorough.

2.3. European Regulatory Framework: The New Regulation

The MDD (Directive 93/42/EEC) was published in 1993 with the goal of harmonizing the laws and standards relating to the design and manufacture of medical devices in the EU, as well as assuring patients that medical devices are safe [3]. Since its publishing, the MDD has remained practically unmodified (except for its amendment by the Directive 2007/47/EC transposed into national law by Decree-law 145/2009) but different guidance documents (MEDDEV) and European standards have been continually revised. Despite this, given the progression in medicine, the legislation governing the placement of medical devices on the EU market needed to be formally updated. This led to the introduction of the MDR.

The MDR does not remove any existing requirements of the MDD, but it adds new ones. The MDD contains 23 articles, whereas the MDR contains 123. Also, there are 12 Annexes in the MDD and 17 in the MDR. The MEDDEV guidance documents applied under the MDD are being replaced by MDCG (Medical Device Coordination Group) guidance documents under the MDR (and the In Vitro Diagnostic Regulation - IVDR). The legal status is the same, with the MDCG guidance documents also not being legally binding. The MDCG is composed by experts of the different Member States (MS) and is chaired by the European Commission (EC).

In the MDR, as previously seen, the definition of a medical device is broader compared to the MDD, bringing more products under the MDR.

Regarding clinical investigations, there are three categories of clinical investigations, namely pre-market clinical investigations (Article 62 of the MDR), post-market clinical investigations (Article 74 of the MDR), and other clinical investigations (Article 82 of the MDR) [1].

For certain high-risk devices (such as implants), Notified Bodies (NB) are now required to consult with an expert panel before placing the device on the market. The expert panel could provide a scientific opinion to the NB on its assessment of the manufacturer's clinical file. Although the NB is not obliged to follow the scientific opinion, it would have to provide a justification for not doing so (Chapter II, Annex IX of the MDR) [1].

The Regulation imposes stricter requirements for the designation of NB, and an increased control and monitoring by National Competent Authorities (NCAs) and the Commission. Stricter requirements have been included for impartiality, independence, and staff expertise (Annex VII of the MDR) [1].

According to the NANDO (New Approach Notified and Designated Organisations) platform, as of September 3, 2021, there are 23 notified bodies designated under the EU MDR (2017/745) and only 6 designated under the EU IVDR (2017/746).

Recently, three Portuguese universities (Coimbra, Aveiro and Beira Interior) signed a partnership for the setup of a NB, to be based at the University of Beira Interior, for conformity assessment of in vitro diagnostic medical devices. This NB will focus on devices that incorporate, use or are controlled by software, sensors or devices that include electronic components, given these devices are not implantable. However, the possibility of this partnership being extended to include other scientific domains or areas of intervention is not ruled out [4].

The MDR also applies to internet sales of MD and the ones used for remote diagnostic or therapeutic services (Article 6) [1]. One of the big changes introduced by the MDR is the Unique Device Identification (UDI) system (Article 27 of the MDR) that pretends to improve the traceability and effectiveness of post-market safety-related activities, requiring that the label of a device bears a globally unique identifier [1]. The other change is the EUDAMED – European Database for Medical Devices, that is planned to have 6 different modules and a public website, promoting transparency, and making data available both in quality and in quantity. The Eudamed functions include the registration of devices and economic operators, as well as the reception of vigilance and field safety reports, that will be essential in the implementation of the MDR, namely in the fulfillment of clinical investigation requirements [5]. Though, Eudamed is not fully operational, and its launch date is planned for May 2022. Manufacturers (and/or sponsors) should review the section 3(d) of Article 123 "Entry into force and date of application" to know which requirements should be addressed according to the AIMDD and MDD until Eudamed is operational. These changes follow FDA's (Food and Drug Administration) UDI and GUDID (Global Unique Device Identification Database).

The MDR also identifies "authorized representative" (Article 11), "importer" (Article 13) and "distributor" (Article 14) as new stakeholders in the lifecycle of a MD [1]. Additionally, it is now specified who should be responsible for regulatory compliance, including who that

person can be, what expertise is required and what obligations that person has (Article 15 of the MDR) [1].

The use of harmonized standards remains voluntary in the MDR. Although, devices that are in conformity with the standards published in the Official Journal of the European Union (OJEU) benefit from a presumption of conformity with the legal requirements. For example, since all manufactures are required to have a Quality Management System (QMS), and ISO 13485:2016 is the only QMS standard on the list published in the OJEU, manufacturers who have implemented this standard can expect the processes related to conformity assessment procedures, affixing of the CE marking and placing on the market, to be quicker and less burdensome [6]. The standards are published and withdrawn from the OJEU by means of Commission implementing decisions (Commission Implementing Decision (EU) 2020/437 of 24 March 2020 and Commission Implementing Decision (EU) 2021/1182 of 16 July 2021). The most common harmonized European standards for medical device manufacturers include:

- EN ISO 13485:2016 – Medical devices – Quality Management Systems – Requirements for regulatory purposes (ISO 13485:2016)
- EN ISO 14971:2012 – Medical devices – Application of risk management to medical devices (ISO 14971:2007)
- EN 62304:2006 – Medical device software – Software life-cycle processes (IEC 62304:2006)
- EN ISO 10993 – Biological evaluation of medical devices
- EN ISO 15223-1:2016 – Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2016)
- EN 60601-1:2006 – Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (IEC 60601-1:2005)
- EN ISO 14155:2020 – Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2020)

The role of the Ethics Committees

Ethics committees (EC) are responsible for evaluating clinical investigations and to determine if ethical principles are being followed. According to Law no. 21/2014 (Chapter IV, Article 16) [7], the CEIC (National Ethics Committee for Clinical Research), or other Ethics Committee designated by the CEIC, must give its opinion on the relevance of the clinical study and its design; the assessment of the anticipated benefits and risks; the protocol and study dissemination materials; the suitability of the Principal Investigator and the other team members; the material and human conditions necessary for conducting the study; the amounts and arrangements for any remuneration or compensation of investigators and subjects, and the relevant elements of any financial contract between the sponsor and the clinical study site; the arrangements for recruitment of subjects; conflict of interest on the part of the sponsor or investigator involved in the clinical study; duration and conditions of clinical follow-up of subjects after completion of the study; procedure for obtaining informed consent; investigator's brochure; quality of facilities; provisions for compensation for injury and damage to health, including death, attributable to the study;

insurance to cover liability of the investigator and sponsor; and rationale for conducting the study involving minors or subjects incapable of giving informed consent.

The Directives and the MDR do not contain any requirements regarding the composition and function of ethics committees. However, Article 62(3) of the MDR mandates that an EC must undertake an ethical assessment in accordance with national legislation, as long as it is compatible with the procedures of the MDR, and that at least one lay person must participate in the assessment [1].

The role of Competent Authorities

Competent authorities (CA) are responsible for evaluating clinical study applications and determining if regulatory requirements are met. The NCA is Infarmed (National Authority for Drugs and Health Products).

Article 72(5) of the MDR stipulates that Member States shall inspect investigation sites to ensure that clinical investigations are carried out in compliance with MDR's requirements and with the clinical investigation plan (CIP) [1]. Therefore, sponsors should ensure that investigation sites are prepared for an inspection. The areas to be inspected are determined by the national law and practices of the CAs.

Article 80 "Recording and reporting of adverse events that occur during clinical investigation" states that "any serious adverse events that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonable possible" shall be reported by the sponsor to all the Member States concerned [1]. This requirement to report only SAEs (Serious Adverse Events) with a causal relationship to the investigational device, comparator or investigation procedure differs from the AIMDD and MDD, which required all SAEs to be immediately reported to all CA of the Member States concerned. Clinical investigations that began before 26 May 2021 may continue to be conducted but the reporting of SAEs must be in line with the MDR (Article 120(11)) [1]. The MDCG issued recommendations on safety reporting under the MDR (MDCG 2020-10/1 – Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 and MDCG 2020-10/2 – Clinical Investigation Summary Safety Report Form v1.0). These guidance documents also cover how safety reports should be submitted to the NCA while EUDAMED is not operational.

2.4. Clinical Studies of Medical Devices

The MDR defines “clinical investigation” as “any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device” (Article 2(45)) [1].

Clinical investigations are classified into three categories (pre-market clinical investigations, post-market clinical investigations and other investigations), each with its own set of requirements. The qualification is determined by the status of the medical device, whether it is CE-marked or not, the usage of the device, whether it is used for its intended purpose or not, and the purpose of the clinical investigation.

Figure 1 can help in determining which MDR Article is applicable for the intended clinical investigation.

The CE certificate (or the declaration of conformity for class I MDs) can help determine whether the MD has a valid CE marking and, consequently, the clinical investigation category.

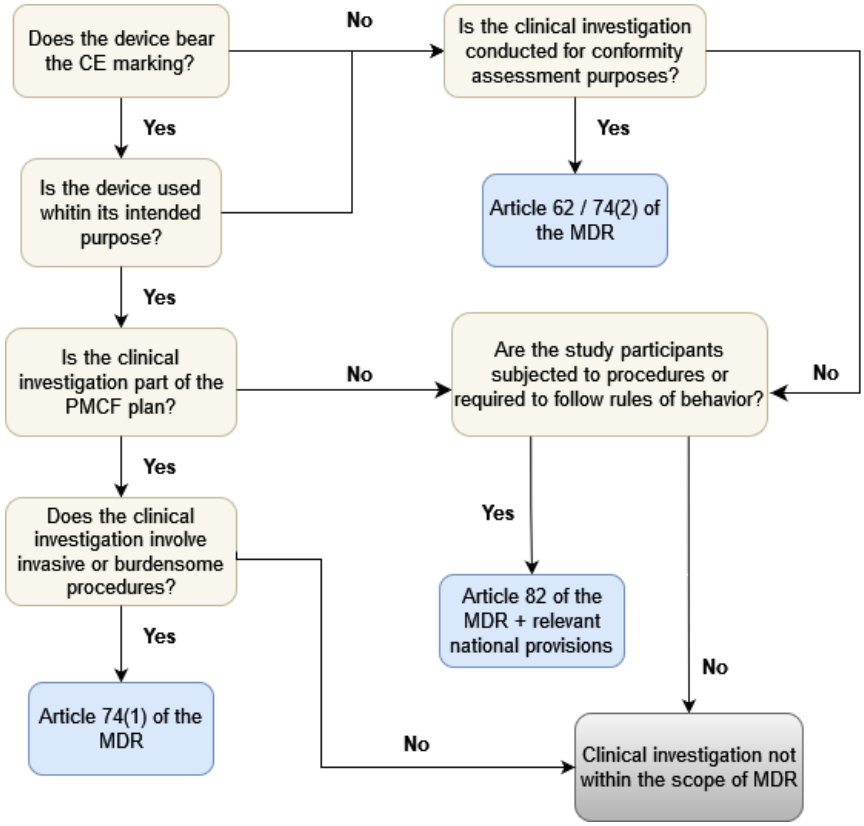

Figure 1 - Flowchart to identify which pathway should be followed to apply for a clinical investigation. Based on the Annex I of the “MDCG 2021-6: Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation” [8].

When a clinical investigation is conducted for conformity assessment purposes, either for a new device (Article 62) or to expand the intended purpose (Article 74(2)), the desired goal is to market the device under the MDR [1]. The prerequisites for Articles 62 and 74(2) are the same. All investigations that are/will be part of the clinical evaluation plan (Article 61

and Annex XVI(A) of the MDR) are considered as investigations for conformity purposes. As a result, early feasibility studies are under Article 62 [1].

Post-market clinical follow-up (PMCF) studies will be contracted by manufacturers and be part of the PMCF plan (Annex XIV(B) [1]. The devices used are part of the patients' standard of care. PMCF studies are termed PMCF investigations if the participants are subjected to procedures considered to be more invasive or burdensome than standard of care. Article 74(1) applies to these PMCF investigations [1].

If the clinical investigation is not conducted for the purpose of conformity assessment and is not part of the manufacturer's PMCF, it will be subject to Article 82 if the participants are subjected to procedures other than the standard of care [1].

2.4.1. Pre-Market Clinical Investigations

Requirements for Pre-Market Clinical Investigations

A pre-market clinical investigation, that is, a clinical investigation with a device not yet CE marked, must adhere to any applicable common specifications (CS), which are defined as a "set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system" (Article 2(71) of the MDR) [1]. A clinical investigation must also follow all the standards imposed by NCA's and ethics committees, the European harmonized standards, and other relevant national and European guidance documents.
Compared to the Directives, the MDR has very detailed requirements for clinical investigations, addressed in Articles 62 through 80, of which can be highlighted [1]:

- general requirements regarding clinical investigations conducted to demonstrate conformity of devices (Article 62)
- informed consent (Article 63)
- clinical investigations on vulnerable populations and subjects (Articles 64 to 68)
- application procedure (Article 70) and assessment by Member States (Article 71)
- conduct of the clinical investigation (Article 72)
- electronic system on clinical investigations (Article 73)

The Article 81 of the MDR covers the implementing acts by the European Commission, which are designed to provide more details on the specific arrangements and procedures required for the implementation of clinical investigations [1].

The Annex XV of the MDR "Clinical Investigations" contains three chapters: Chapter 1 of General Requirements; Chapter 2 of the Documentation Regarding the Application for Clinical Investigation; and Chapter 3, with Other Obligations of the Sponsor [1]. The Directives (AIMDD and MDD) specified the requirements for clinical investigations in one article (Article 10 of the AIMDD and Article 15 of the MDD) and in parts of the Annexes 6 and 7 of the AIMDD and Annexes VIII and X of the MDD [2,3].

Despite the detailed requirements, experienced sponsors may know these requirements well because they are outlined in the European harmonized standard, EN ISO 14155:2011,

Clinical investigation of medical devices for human subjects – Good Clinical Practice, and in the Directives guidance documents, namely MEDDEV 2.7/4, Guidelines on Clinical Investigation: a Guide for Manufacturers and Notified Bodies; MEDDEV 2.7/2 Rev. 2, Guidelines for competent authorities for making a validation/assessment of a clinical investigation application under Directives 90/385/EEC and 93/42/EC; and MEDDEV 2.7/3 Rev. 3, Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and 93/42/EEC. The requirements in the MDR for clinical investigations were deliberately based on the international standard ISO 14155:2011, to facilitate the recognition of the results of clinical investigations carried out within the EU by other countries outside the EU, and vice versa.

Related to the conduct of clinical investigations, the MDR introduced new requirements. The term “sponsor” was introduced, meaning “any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation” (Article 2(49)) [1]. Under the Directives, only the manufacturer (or authorized representative) was acknowledged as responsible for the conduct of a clinical investigation (Article 15(1) of the MDD)[3]. As a result, there was some uncertainty about the regulatory responsibilities of an independent investigator who initiates a clinical investigation.

Regulatory Purpose of a Pre-Market Clinical Investigation

Pre-market clinical investigations are often carried out for conformity purposes (for CE marking). According to Annex XIV, Part A, Section 1(a) of the MDR, the clinical evaluation plan must include: “a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility, and pilot studies, to confirmatory investigations, such as pivotal clinical investigations” [1]. The Annex I “Clinical development stages” of the new ISO 14155:2020 may be useful in the determination of types of investigations associated with different clinical stages [9].

Furthermore, the conduct of a clinical investigation for the purpose of CE marking is closely connected to the criteria in Article 61 of the MDR “Clinical evaluation”, since it states that confirmation of conformity with relevant General Safety and Performance Requirements (GSPRs) in Annex I, evaluation of undesirable side-effects, and the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 (GSPR 1 and 8), must be based on clinical data that provides sufficient clinical evidence. The GSPR 1 demands that devices perform as intended by the manufacturer, that they are safe and effective, and that any risks associated with their use are acceptable when weighed against the benefits. According to GSPR 8, all known and predictable risks, as well as any undesirable side-effects, must be minimized and acceptable when weighed against the estimated benefits to the patient and/or user under normal usage conditions [1].

The regulatory aim of the clinical investigation for CE marking purposes is to generate clinical data that meets the identified GSPRs. The manufacturer determines if other GSPRs will need confirmation of its conformity, with clinical data. Depending on the GSPRs identified, the objectives of clinical investigation will need to be properly addressed.

QMS and Pre-Market Clinical Investigations

The majority of manufacturers would most likely demonstrate MDR compliance by conformity assessment based on a QMS and technical documentation evaluation, as described in Annex IX of the MDR [1]. For the assessment of the QMS system, a description of "the procedures and techniques for monitoring, verifying, validating and controlling the design of the devices and the corresponding documentation as well as the data and records arising from those procedures and techniques" must be submitted (Section 2.2(c) of Annex IX of the MDR) [1]. These procedures and techniques are the strategy for regulatory compliance, the identification of applicable GSPRs, the risk management, the clinical evaluation (including PMCF), the solutions for fulfilling the applicable specific requirements regarding design and construction and the information to be supplied with the device, and the management of design or QMS changes.

2.4.2. Post-Market Clinical Follow-up Investigations

Requirements for PMCF Investigations

A post-market clinical follow-up (PMCF) investigation is defined by Article 74 of the MDR ("Clinical investigations regarding devices bearing the CE marking"), as a clinical investigation undertaken to assess, within its intended purpose, a device which already bears the CE marking [1].

A PMCF investigation must be distinguished from other types of PMCF activities, such "as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data" or "evaluation of suitable registers" (Annex XIV of the MDR, Part B) [1].

The requirements to conduct PMCF investigations are specified in Article 74, with some overlapping with those applicable to pre-market clinical investigations. To comply with Article 74 of the MDR, it is critical to determine whether the PMCF investigation will be conducted exactly according with standard practice and the device's Instructions for Use (IFU), or whether additional procedures (such as blood analyzes or imaging) are planned, and, if those procedures are considered invasive or burdensome [1].

According to the guidance document "MDCG 2021-6" [8], an additional burdensome or invasive procedure is a procedure additional to those performed under the normal conditions of use of the device. This may include additional imaging, patient questionnaires, additional clinical or hospital visits, and venipuncture.

The new ISO 14155 features a new annex (Annex I, Clinical development stages) with a section dedicated to "Burden to subjects", that gives details on the classification of clinical investigations [9].

Regulatory Purpose of a PMCF Investigation

The MDR requires that the post-market surveillance (PMS) plan includes a PMCF plan or a justification of why a PMCF is not applicable (Annex III of the MDR "Technical Documentation on Post-Market Surveillance, Section 1.1) [1].

A PMCF should be performed if, after an adequate premarket clinical evaluation, there remains residual risks and/or uncertainties (MEDDEV 2.12/2 rev2)[10]. According to Annex XIV, Part B, Section 6.1. of the MDR, a PMCF investigation should be performed with the aim(s) of "confirming the safety and performance of the device throughout its expected lifetime; identifying previously unknown side-effects and monitoring the identified side-effects and contraindications; identifying and analyzing emergent risks (…); ensuring the continued acceptability of the benefit-risk ratio (…); identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct". The aim(s) should be documented in the PMCF plan, and its required elements are stated in Section 6.2 [1].

QMS and PMCF Investigations

The results of PMCF investigations must be registered in the PMCF evaluation report. These results shall also be taken into account for the clinical evaluation report, risk management, PMS report, PSUR (Periodic Safety Update Report) and may even identify the need for preventive and/or corrective actions (Annex XIV of the MDR, Part B, Section 8, "Post-market clinical follow-up") [1].

2.4.3. Other Clinical Investigations

Requirements Regarding Other Clinical Investigations

Article 82(1) of the MDR on the "Requirements regarding other clinical investigations", states that clinical investigations that are not undertaken for any of the objectives specified in Article 62(1) (Figure 1) must follow Article 62 paragraphs 2 (the need for a legal representative), 3 (ensure the rights, safety, dignity, and well-being of the participants), 4 (list of the conditions that must be met to conduct a clinical investigation) and 6 (the investigator and the personnel involved in the conduct of a clinical investigation must be qualified)[1,9].

Moreover, Article 82(2) states that, in order to protect the rights, safety, dignity and well-being of participants, as well as the scientific and ethical integrity of clinical investigations, each Member State (MS) must define supplementary requirements for such investigations, implying that manufacturers must look for and comply with any national provisions [1].

2.4.4. Conducting Successful Clinical Investigations

Experienced Clinical Personnel

Given that clinical investigations may be complex, and that the data generated are needed to be ethically and scientifically reliable and robust, it is important to delegate responsibilities to knowledgeable personnel [7,9].

Unlike many pharmaceutical studies, the success of a medical device clinical study is determined by the clarity of the clinical investigation plan/protocol in describing how the medical device should be studied, the IFU, the competence of the health professionals and

in the ability of a layperson to use the device [9]. Thus, when sponsors lack expertise, it may be wise to outsource specific activities/responsibilities to avoid committing mistakes that may threaten the success of a market entry or the continuous presence on the market of a certain device.

Clinical Investigation SOPs

Standard Operating Procedures (SOPs) are “detailed, written instructions to achieve uniformity of the performance of a specific function” [11]. The sponsors need to develop SOPs to guarantee compliance with the Regulation, the EN ISO 14155, the MDCG guidance documents and with other applicable standards and provisions of countries where a clinical study is to be conducted.

The SOPs to be developed depend on whether sponsors intend to perform all study activities in-house, or whether they intend to outsource activities for which they lack expertise. Sponsors may also outsource all development and management activities to Contract Research Organisations (CROs) or Clinical Trial Units (CTUs). By choosing to outsource one or more activities, fewer internal SOPs may be needed, as long as those of the external vendor are used [9].

Sponsors may develop the following clinical study conduct SOPs for the activities managed in-house [9]:

- CIP/protocol development and amendment
- Informed Consent Form development
- Investigator Brochure (IB) development
- Selection and Site qualification
- Vendor Qualification, Selection and Management (Contract Research Organization, central laboratory, etc.)
- Site Monitoring
- SAE Reporting
- Medical Device Accountability
- Data Collection and Management
- Regulatory authority submission process
- Conduct of the clinical study (procedures, staff qualifications, etc.)

These standard procedures should be developed and controlled within the sponsor’s Quality Management System (QMS). When outsourcing certain activities, the sponsor must guarantee that the vendors are experienced in medical devices and work under a QMS.

2.4.4.1. Planning a Clinical Investigation

Elements of the Planning Process

A well-structured planning approach is important to understand what must be done and when, whether activities should be done sequentially or can overlap to save time, and who is responsible for each activity. Clinical investigation planning of medical devices is

addressed in depth in the new EN ISO 14155:2020 [9]. An example of a method for planning a clinical study, including the activities that should be carried out before the study start, during study and close-out, is presented in Table 1.

Table 1 - Example of the activities in a plan for a clinical investigation. Retrieved from "Medical device clinical investigations – What's new under the MDR? [9]

Set-up phase	**Enrollment phase**	**Close out phase**
Project team setup	Training and site initiation	Site close out
Purpose & study design	Monitoring	Document archiving
Project management	Data collection and management	Statistics
Vendor selection	Adverse events & device deficiencies	Clinical study report
Development of CIP	Protocol deviations	Publications
Site selection	Device accountability	
Other regulatory/clinical documents	Audits	
Site agreements & EC/CA submissions		
Device release for clinical study		

Purpose of the Clinical Investigation

Most clinical investigations are conducted for regulatory purposes, although this is not always the case. Therefore, the purpose of the investigation should be defined at the beginning of the planning phase because it will affect the study design and the clinical data that must be gathered [9].

Project Team Members

The members of the project team must be identified, along with their roles, responsibilities, and qualifications, that can be based on education or experience. The roles differ but generally the clinical research team at, or representing, the sponsor include the clinical project manager, regulatory and start-up specialist, biostatistician, data manager and monitor.

The Clinical Project Manager (CPM) is responsible for the oversight of all pre-study, on-study, and close-out activities. They monitor the progress of the project(s) and provide updates to internal (and external stakeholders, if applicable), such as the sponsor/client. The CPM ensures that project deliverables are provided on time and within budget [12].

Some responsibilities/clinical tasks of a CPM include:

- Initiate and manage clinical studies in accordance with the ICH-GCP guidelines and other relevant guidelines, legislation and SOPs;
- Monitor the progress of the clinical study in relation to the project plan and regulatory policies;

- Identify risks and develop and implement plans to mitigate risks in collaboration with other team members and stakeholders;
- Act as a daily point of contact for the sponsor and all members of the project team;
- Manage the development of the clinical protocol, IB, ICF, CRFs and other clinical materials;
- Supervise and mentoring study monitors;
- Review clinical data, monitoring and adverse event reports;
- Ensure all project members have the required resources to complete their assigned tasks;
- Report the progress to the internal project team, the internal and, if applicable, external stakeholders;
- Negotiate contracts with study sites and suppliers/vendors;
- Manage project finances in accordance with the (sponsor) contract and budget;
- Provide input for proposals and budgets.

The Regulatory and Start-Up Specialist supports regulatory activities during the start-up phase of clinical studies.

The activities of the Regulatory and Start-Up Specialist may include:

- The review of clinical protocols, ICF and other clinical documents and materials, ensuring that these documents were developed according to relevant guidelines and regulations;
- The preparation of documents for submission to ethics committees and competent authorities;
- Serve as a point of contact between the sponsor and authorities;
- Support internal quality audits and regulatory inspections;
- Perform quality control of documents provided by study sites.

The biostatistician is responsible for collecting, analyzing, summarizing, presenting, and interpreting clinical data. Their responsibilities include:

- Development of Statistical Analysis Plans (SAP);
- Conduction of statistical analysis as specified in the SAP;
- Assist with protocol development, sample size calculation, randomization lists;
- CRF review to ensure that primary and secondary endpoints are collected properly;
- Draft or review clinical study reports and statistical reports;
- Produce tables, listings and figures (TLF);
- Assist with preparation of abstracts and presentations.

Data Collection and Management

Clinical data from clinical investigations are collected on a case report form (CRF), which, according to ICH GCP E6 (R2) is “a printed, optical, or electronic document designed to record all of the (…) information to be reported to the sponsor on each trial subject” as required by the protocol/CIP [11]. Data management refers to the process of cleaning and management of the collected subject data, in compliance with regulatory provisions [13].

Except for requiring that data management should be in the CIP, the MDR has no specific requirements for CRFs or data management. The specific details regarding CRFs and data management are provided in EN ISO 14155:2020 [9].

Clinical Data Management (CDM) is the work performed on data from the preparation to collect that data through the time it is extracted for final analysis. CDM leads to generation of reliable and statistically sound data from clinical studies. For this, it comprises various procedures such as CRF designing, CRF annotation, data entry, database design, data validation, medical coding, discrepancy management, data locking as well as data extraction [13].

Study Monitoring

Appropriate monitoring is an obligation under the MDR (Article 72(2) of the MDR) [1]. Sponsors designate monitors, that must be independent from the study sites, to oversee the course of a clinical investigation and verify that it is being conducted in accordance with the Clinical Investigation Plan (CIP), the GCPs, EN ISO 14155 and other relevant requirements (Section 4 of Chapter III, Annex XV)[1].

The Clinical Investigation Plan (CIP) is defined as “a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organization and conduct of a clinical investigation” (Article 2(47) of the MDR)[1].

The ICH GCP E6 (R2) guideline defines monitoring as “the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)” [11]. The purpose of monitoring is to ensure that the rights and well-being of the participants are protected, and that the data collected are accurate, complete, and verifiable from the source documents [11].

To guarantee a successful monitoring, the SOPs (and other procedures specified by the sponsor for monitoring) should be developed considering the monitoring procedures stated in EN ISO 14155 [9]. The monitor must be qualified and follow the sponsor SOPs related to monitoring, and the monitoring plan, that describes the monitoring activities for that specific study. Monitors should keep in touch with study sites on a frequent basis to verify that study requirements are being met and any deviations are addressed promptly. A risk-based monitoring must be considered, in which the monitoring plan is based on the minimization of risks that could interfere with the collection of essential data or the conduct of study activities [11].

According to Section 6, Chapter III, Annex XV of the MDR, sponsors are required to show that the clinical investigation is being carried out in accordance with GCPs, by internal or external inspections [1]. The Directives did not mention this provision.

The Clinical Research Associate (CRA) or study monitor is responsible for the execution of various activities in the study, including:

- Study setup and manage communications with study sites;
- Administer protocol and related study training to study sites personnel;

- Perform site selection, initiation, monitoring and close-out visits;
- Write monitoring reports;
- Ensure subject safety and review source documents for adverse events;
- Guarantee the adequacy, reliability and quality of the data collected from study sites.

Development of CIP/Protocol

The clinical investigation plan (CIP) must include the rationale, objectives, design, ethical aspects, monitoring and quality measures, inclusion and exclusion criteria, target populations, treatment schedules, follow-up duration, concomitant treatments, conduct, record-keeping, and statistical plan for a clinical investigation (Whereas statement #47 and Chapter II of Annex XV, of the MDR) [1]. It should be a controlled document, ensuring that only up-to-date versions of the document are in place and thus avoiding misunderstandings that might cause delays in the study. The CIP also needs to be signed by each Principal Investigator and the sponsor.

The information that must be included in the CIP is specified in Annex XV, Section 3 of the MDR [1].

One of the steps for a successful clinical investigation is the definition of the objectives, generally aligned with the clinical development strategy (within the clinical development plan). In clinical investigations with MDs, the objectives relate to the clinical performance, clinical benefit(s), efficacy, and clinical safety aspects of the device. The clinical performance is the ability of a device to achieve its intended purpose, thus leading to a clinical benefit (Article 2(52) of the MDR) [1]. Clinical benefit is the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health (Article 2(53) of the MDR) [8].

Selection of Study Site(s)

Site selection is an important part in the planning of a clinical study since low recruitment, and poor data quality may come from poor site selection [14].

When selecting a site, it is recommended to, at least, check the availability of potentially eligible subjects, the adequacy of equipment and infrastructures, and the familiarity of site personnel with GCPs [9].

Other Study Related Documents

Other relevant study related documents that must be made available during this phase include the informed consent form (ICF), case report from (CRF), instructions for use (IFU), investigator's brochure (IB), statistical analysis plan, risk management documentation, insurance documentation, and agreement between the sponsor and investigational site(s)[9].

The informed consent is the "process by which an individual voluntarily confirms willingness to participate in a particular clinical investigation, after having been informed of all aspects

of the investigation that are relevant to the decision to participate" [15]. In case of minors or incapacitated subjects, it also may be "an authorization or agreement from their legally designated representative" (Article 2(55) of the MDR) [1].

The instructions for use (IFU) are "the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken" (Article 2(14) of the MDR) [1]. The minimum content of IFU, aside from information about the product (name, product ID) and the manufacturer (name, address, contact information), is detailed in Annex I of the MDR, Chapter III, Section 23.4 [1]. The instructions for use must be provided together with the device. Exceptionally, IFU are "not required for Class I and Class IIa devices if such devices can be used safely without any such instructions" (Annex I of the MDR, Chapter III, Section 23.1(d)) [1].

The investigator's brochure (IB) is a "compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation" [15]. The MDR specifies the information to be in the IB in Annex V of the MDR, Chapter II, Section 2.1. The IB may help investigators in giving detailed information for patients (e.g. during the process of obtaining the informed consent), in identifying and classifying adverse events (e.g. determining if an adverse device effect is already known and thus anticipated or unanticipated) and in providing information on the use of the medical device (e.g. cleaning, calibration and maintenance) [1].

2.4.5. Application for clinical investigations

Until EUDAMED is fully operational, the application for clinical studies with medical devices should be made through the applicable national procedures. In Portugal, the Infarmed decided that the sponsors need to follow the provisions in the MDR related to general requirements, documentation for submitting applications/notifications and deadlines [16]. Until now, it was necessary to submit two different dossiers through RNEC (National Clinical Trials Registry), one that would be evaluated by the CEIC, and the other by the Infarmed. From 26 May 2021 and until EUDAMED is operational, the submission is made through the RNEC portal (www.rnec.pt) and only to the Infarmed, which liaises with the CEIC in the evaluation of the applications. Also, while the implementing act of the MDR is not published, the provisions of the national legislation continue to apply to fees, administrative offences, the national electronic system (RNEC), and the opinion of the Ethics Committee [7,16].

According to Article 70 of the MDR, the sponsor of a clinical investigation must submit the application to the Member State(s) concerned, accompanied by the appropriate documentation. The documentation that must be submitted is referred in Chapter II of Annex XV. Once EUDAMED is operational, when submitting the application, the system should generate a Union-wide unique single identification number for the clinical investigation, which shall be used for all relevant communication related to that investigation. The Infarmed must notify the sponsor within 10 days (or 15 days) of receiving the application whether the clinical investigation falls within the scope of the MDR and whether the dossier is complete. After this notification, the sponsor has 10 days (or 20 days, if the Member State concerned extends this period) to update or change the documentation, if necessary. Then,

the Member State concerned notifies the sponsor within 5 days (or 10 days) whether the clinical investigation falls under the scope of the MDR and whether the application is complete. During the assessment period, the Member State may request additional information from the sponsor.

In the case of investigational class I devices or non-invasive class IIa and class IIb devices, the sponsor may start the clinical investigation, unless otherwise stated by national law, immediately after the validation date of the application, and only if an ethics committee in the Member State concerned has not rendered a negative opinion (Article 70(7) of the MDR) [1]. In the case of other investigational devices, the clinical investigation may start after the Member State notifies the sponsor of its authorization and if there isn't a negative opinion from an ethics committee. Within 45 days of the validation date, the Member State notifies the sponsor of the authorization. This period may be extended for an additional 20 days, for the Member State to consult with experts.

Among the documents to be provided by the sponsor to apply for a clinical investigation, the following are mandatory:

- Cover letter
- Application form
- Investigator's Brochure (IB)
- Clinical Investigation Plan (CIP)
- CIP synopsis
- Statement of conformity (not mandatory as a statement of conformity is included at the end of the application form)
- Example of labels
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data/personal information
- List of General Safety and Performance Requirements (GSPR)

Also, depending on the clinical investigation, the following may or may not be required:

- Risk management documentation (can be included in the IB)
- Test reports (can be included in the IB)
- Proofs of Clinical Investigation Insurance
- Suitability of investigational sites and investigation site team
- Manufacturer's Instructions for Use (IFU) (for non-CE marked devices, this document should be included in the dossier, if available. If it is not available, a detailed description of the medical and/or surgical procedure and handling of the device must be provided in the CIP)
- Suitability of the Investigators
- Recruitment procedures and advertising materials (can be included in the CIP but should also be provided as separate documents for clarity reasons)
- Documents to obtain informed consent, informed consent procedure, all written information to participants, payments, and compensation of participants (can be included in the CIP but should also be provided as separate documents for clarity reasons)

- Notified Body Certificates (If the device bears a CE-mark, a valid copy of the CE-certificate issued by a notified body must be provided)
- Decisions from other countries
- PMCF plan (only for PMCF investigations)
- Expert panel opinion

For PMCF investigations (investigations involving CE-marked devices, to be used within the scope of its intended purpose) involving additional burdensome or invasive procedures, there is no need for an approval, but the sponsor shall notify the competent authority at least 30 days prior to its start, submitting the appropriate documentation mentioned above.

Once Eudamed is fully functional, it will be possible to submit an application for a coordinated assessment for clinical investigations (Article 78 of the MDR) [1]. This is a voluntary procedure until 26 May 2027, when it will become mandatory. A sponsor may submit, by means of EUDAMED, a single application for a clinical investigation to be conducted in more than one MS. The sponsor must designate one of the MS in which the clinical investigation is to be conducted to perform as a coordinating MS. Within six days from the application's submission, the MSC shall decide which MS will act as coordinating. If they do not reach a consensus, the coordinating MS proposed by the sponsor must assume that role. Under the direction of this coordinating MS, the Member States involved coordinate their assessment of the application. However, the completeness of the documentation related to clinical investigator and investigational site's capacity to conduct the clinical investigation, the opinion(s) of the ethics committee(s), the proof of insurance and the documents to be used to obtain informed consent (sections 1.13, 3.1.3, 4.2, 4.3 and 44 of the Chapter II of Annex XV, respectively) are to be assessed individually by each Member State [1]. Each Member State concerned (MSC) may request, only once, additional information from the sponsor. The latter shall submit the requested information within the timeframe established by the MS, which cannot exceed 12 days from the date of receipt of the request.

Within 7 days of the notification date, every consideration submitted by a Member State must be considered by the coordinating MS. Within 10 days of the notification date, the coordinating Member State assesses if the clinical investigation falls under the scope of the MDR and whether the application is complete, and notifies the sponsor. Then, within 26 days of the validation date, the coordinating Member State shall establish the results of its assessment in a draft report to be transmitted to the other Member States. By day 38 after the validation date, the other States concerned must transmit their comments and proposals on the draft assessment report to the coordinating MS, who must take these comments and proposals in account in the final assessment report, to be transmitted within 45 days of the validation date to the sponsor and to the other MS concerned.

3. Case Studies

This section presents two case studies, where some of the theorical knowledge acquired during the internship is presented. The first one, named “Non-invasive brain stimulation research in chronic pain” is based on one activity carried out during the internship (described in the section “4.3. Activities carried out during the internship”) in which the aim was to review what had already been done in chronic pain with transcranial magnetic stimulation (TMS). This case study also explores tES (transcranial electrical stimulation) techniques that are being used in chronic pain.

The second case study “Ethical and Regulatory Issues Associated with the Use of NIBS Devices” derives from an activity that aimed to review the regulatory framework of TMS, also exploring other concepts that should be considered when designing clinical studies and when placing non-invasive brain stimulation devices on the market.

3.1. Case Study: Non-Invasive Brain Stimulation Research in Chronic Pain

3.1.1. Non-Invasive Brain Stimulation Devices

Non-Invasive Brain Stimulation (NIBS) refers to a set of specific techniques and technologies with which the excitability of certain brain areas can be modulated without penetrating the skin or a body cavity. The two main modalities of this non-invasive neuromodulation are Transcranial Magnetic Stimulation (TMS) and transcranial Electrical Stimulation (tES)(Figure 2) [17].

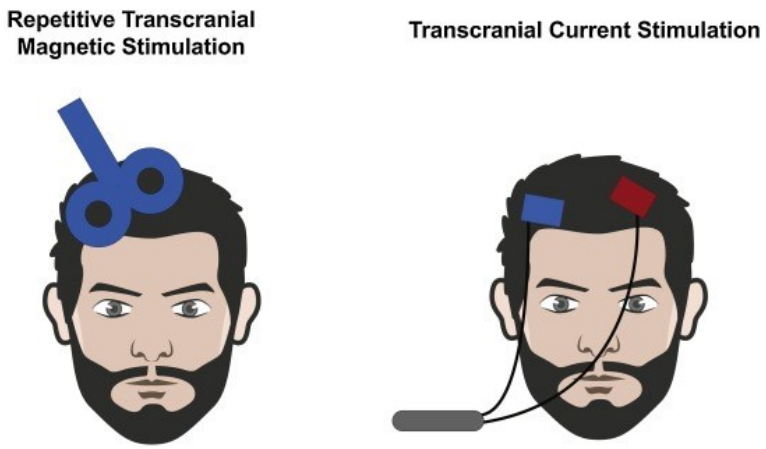

Figure 2 - Main techniques of non-invasive brain stimulation. (Adapted from Madrid & Benninger (2021) *[18]*. Under a CC BY-NC-ND license).

Since NIBS devices are non-invasive, active, and intended to “administer” energy, they will be considered moderate risk and thus Class IIa, according to the classification rule 9, Annex IX of the MDR [1].

Transcranial Magnetic Stimulation

TMS is a neurophysiological technique that allows a painless and non-invasive stimulation of the human brain through the scalp. This technique consists of using a device that

produces an electromagnetic field, conducted through a coil that is placed on the individual's scalp. The electromagnetic field generated is able to cross the skull and the meninges, stimulating/inhibiting an area in the cerebral cortex through electromagnetic induction. The cortical excitability or inhibition depends on whether high (> 1 Hz) or low (≤ 1 Hz) frequency stimulation is used, respectively [19].

TMS can be used, in either single or repetitive pulses, to temporarily disrupt the behavior of a cortical area, resulting in "virtual lesions", that allow to study the function of that area [20].

Currently, there are at least four types of TMS – rTMS (repetitive TMS), dTMS (deep TMS), iTBS (intermittent TBS) and aTBS (accelerated TBS). Deep TMS is similar to rTMS but uses a H-shaped coil instead of the figure-of-eight coil used in rTMS, allowing for the stimulation of deeper brain structures. iTBS is delivered through a figure-of-eight coil, like rTMS. The difference between the two is the frequency (typically 50 Hz) and the duration of stimulation, which is much shorter in iTBS (20 minutes vs 3 min). aTBS differs from iTBS in the number of sessions applied per day. In aTBS, 10 sessions a day can be applied, reducing the total duration of the treatment [21].

In the European Union, there are already several TMS devices with CE marking, i.e., they are approved for marketing for a number of indications, including major depressive disorder (MDD), Autism Spectrum Disorder (ASD), Alzheimer's disease, stroke, Parkinson's, smoking cessation, obsessive compulsive disorder and fibromyalgia [22,23].

Transcranial Electrical Stimulation

tES, also known as transcranial Current Stimulation (tCS) applies weak electrical currents (~1-2 mA) to the scalp to stimulate the cortex, usually via two or more electrodes. tES includes different techniques, namely tDCS, tACS and tRNS [24]. tDCS uses constant currents while tACS and tRNS use oscillating and randomly alternating currents, respectively (Figure 3) [25].

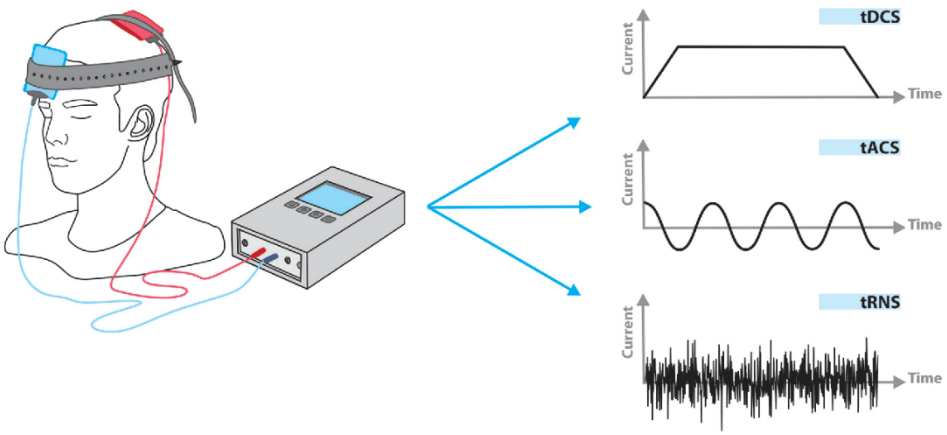

Figure 3 - The currents applied in tES can be direct (tDCS), alternating (tACS) or random (tRNS). (From Yavari et al., 2017 *[25]*. Under a CC BY license).

The most popular variant of tES is tDCS — given that it is relatively inexpensive to acquire or create —, that applies a weak direct current between electrodes mounted on the head, which partially passes through the cortical tissue and affects relatively large cortical areas. This current de- or hyperpolarizes neuronal resting membrane potentials and thereby alters cortical excitability. The primary effects of tDCS do not include synaptic mechanisms but instead involve voltage-dependent ion channels [26].

The electrode placement is considered important: when the anode (positive electrode) is placed over a specific brain area, the current flows into that region, increasing cortical excitability — stimulating neuronal activity. The cathode (negative electrode) is the exit point of the current, inhibiting neuronal activity (decrease of cortical excitability due to hyperpolarization of cortical neurons) [27].

3.1.2. Chronic Pain definition

Chronic pain can be defined as pain that is recurrent or persists past normal healing time, lasting longer than 3 months [28]. According to the ICD-11 classification system, the "chronic pain" category can be divided into 7 groups: chronic primary pain (from an unknown source), chronic cancer pain, chronic posttraumatic and postsurgical pain (that develops after tissue injury or after a surgical procedure), chronic neuropathic pain (involving the somatosensory nervous system), chronic headache and orofacial pain, chronic visceral pain (from the internal organs), and chronic musculoskeletal pain (affecting the bones, joints, muscles or other soft tissues)[28].

It can also be divided into nociceptive, neuropathic or nociplastic [29]. Nociceptive pain is caused by ongoing inflammation and damage of non-neural tissues and is the most common type of chronic pain, including arthritis and various forms of spinal pain [29]. Neuropathic pain is caused by nerve damage and is associated with numbness and allodynia (pain due to a stimulus that usually does not provoke pain), and constitutes approximately 15-25% of cases, including conditions like diabetic neuropathy and postherpetic neuralgia [29]. Nociplastic pain is characterized by abnormal processing of pain signals in the absence of tissue damage or other pathology involving the somatosensory system, and comprises disorders like fibromyalgia, irritable bowel syndrome and non-specific back pain [29]. The mechanisms underlying nociplastic pain are still uncertain, however they may include increased central nervous system (CNS) pain and sensory processing (central sensitization) as well as altered pain modulation. Like other diseases, it is linked to disease-specific changes in both the peripheral and central nervous systems, along with other CNS-derived symptoms, including fatigue and mood and sleep problems [29].

3.1.3. Prevalence of Chronic Pain

The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 revealed that pain and pain-related disorders are the leading cause of disability and disease burden throughout the world. Recurrent tension-type headaches were shown to be the most

frequent symptomatic chronic condition, affecting 2.3 billion people worldwide. Also, low back and neck pain have continuously been the primary causes of disability worldwide [30].

In Portugal, it is estimated that 37% of the adult population suffers from chronic pain. The most-reported pain location is the lumbar region, representing 42% of the subjects. Females, older people, and those with a lower socioeconomic status seem to be the most affected. Also, Portuguese chronic pain subjects have a high pain-related disability, high impact on emotional status and high work-related impact [31].

3.1.4. Pharmacotherapy and Non-pharmacological Options

Guidelines typically recommend a multimodal approach, which might include pharmacotherapy and non-pharmacological options, including psychotherapy, complementary and alternative treatments, and invasive procedures. Although there are several pharmacological treatment options for chronic pain, about 30% of patients remain symptomatic [32]. Besides, the drugs used generally have limited long-term effectiveness, unwanted side effects and show potential for addiction (in the case of opioids)[33].

Aside from abuse and addiction, the lesser-known risks of chronic opioid use therapy include immunosuppression, sleep apnea, osteoporosis, hormonal changes including reduced fertility and sexual dysfunction, and an increased risk of myocardial infarction[34].

Non-opioid pharmaceuticals generally used include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, antidepressants (typically serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressants) and anxiolytics[35].

Non-pharmacological approaches include therapeutic exercise, transcutaneous electric nerve stimulation (TENS), massage therapy, therapeutic ultrasound, and behavioral therapies, such as cognitive behavioral therapy and mindfulness [35].

At the economic level, chronic pain shows large direct and indirect costs to healthcare services. According to Azevedo and colleagues (2016)[36], each patient costs the healthcare service €1,883.30 (42.7% direct costs and 57.3% indirect costs). These data show the need for further research and the pursuit of new interventions for the prevention and treatment of chronic pain.

Among new alternatives, NIBS are promising treatments in alleviating pain. These techniques have a potential advantage over conventional treatments because they directly affect central neural targets, therefore having a stronger effect on central sensitization [37].

3.1.5. The Evidence on NIBS

TMS

In what concerns chronic pain, for TMS, the evidence is conflicting, with some papers reporting benefits, while others report no change [38]. The latest systematic reviews and meta-analyses show that single doses of high-frequency rTMS applied to the motor cortex may present short-term effects [32,38–40]. Also, TMS has evidence of definite efficacy for

chronic neuropathic pain (Level A evidence) and probable efficacy for fibromyalgia (Level B evidence)[41].

When administered within recommended guidelines, TMS (including its variants) is safe and well-tolerated, with some mild side effects and only rare serious adverse effects [42]. The most reported adverse events are transient headaches and neck pain. Serious adverse events include seizures (with an incidence of 0.1-0.6%, comparable to that of most psychotropic medications), hearing impairment and mania [42].

The contraindications of TMS include intracranial metallic or magnetic implants, pacemakers and other implantable MDs, history of seizures, history of serious head trauma, and pregnancy. A screening questionnaire to implement before TMS is available [43], allowing physicians and investigators to weigh the benefits and risks of this procedure to the subjects.

tDCS

Five meta-analyses reported positive statistically significant results, with effect sizes ranging from 0.51 to 1.9 (considering moderate effect >0.5 and large >0.8). These studies have focused on specific chronic pain disorders, like fibromyalgia, migraine, and low back pain [44–48].

Despite the positive results of tDCS in numerous studies, clinical recommendations have only been made for fibromyalgia (level B of evidence – probable efficacy) and lower limb pain due to spinal cord injury (level C of evidence – possible efficacy) [49].

tDCS has only mild and transient side effects. When systematically assessed, the incidence of common adverse events was not different between the active and sham arms of the studies, and included discomfort, itching, headache and burning sensation [50].

The occurrence of skin reddening (tDCS-induced erythema) is substantially higher in active arms and is thought to be caused by an increase in blood flow through skin vessels as a result of the current application. Despite being often benign, it can affect study blinding and should be diminished by following the standard procedures of tDCS application[50].

The use of tDCS only resulted in skin burns when standard procedures were not followed (such as humidification of sponges and limit of current over a maximum impedance)[50].

tACS

The use of tACS for the treatment of chronic pain syndromes is still far from being a reality, as only 2 clinical studies have been conducted [51,52]. However, these studies have promising results. Arendsen et al. (2018)[52] (N = 26 participants) found that tACS at alpha frequency can significantly reduce pain when compared to sham stimulation. Ahn et al. (2019)[51] (N = 20 participants) in a crossover, sham-controlled study also found that increasing alpha oscillations with tACS in the somatosensory regions correlates with pain relief in chronic low back pain.

tRNS

Regarding tRNS, two randomized sham-controlled studies were found. One study [53] used a cross-over design and another [54] a parallel design. Palm et al. (2016)[53] (N = 16 participants) compared the effect of tRNS (over M1 contralateral to most painful side) with sham in multiple sclerosis related neuropathic pain. Both tRNS and sham groups showed no statistically significant changes in mean pain VAS (visual analog scale) score before and after treatment. However, the study was conducted in a small sample size over a short stimulation period. Curatolo et al. (2017)[54] (N= 20 participants) investigated the effects of M1 tRNS in fibromyalgia. Active tRNS of M1 resulted in an overall improvement of symptoms, with a significant reduction in pain, when compared to sham.

3.1.6. Future Research

Regarding TMS and chronic pain disorders, further well-designed studies with longer courses of stimulation and large sample sizes will allow the drawing of more accurate conclusions. Future studies should also collect patient reported outcomes of quality of life (QoL) and treatment satisfaction. Neuronavigation is highly recommended to define the best stimulation targets [55].

Personalizing tDCS might improve its efficacy given the anatomical and functional heterogeneity of stimulated neuronal structures, the heterogeneity of concomitant medication, and the heterogeneity of psychiatric conditions. These various heterogeneities might be to blame for negative findings or negative synergies [56].

New research lines are trying to increase NIBS efficacy by using computational models, considering state dependency, and applying closed-loop technologies[1] [41,56]. There is growing evidence that computational models may be used to modulate the intervention and tailor it to differences in individual responses [57] and in electrical current distribution. These models can give information to personalize protocols, such as stimulation intensity or modification of electrode montages (in case of tES) [56]. Also, evidence suggests that the activity level of the stimulated cortical areas influences the effects of NIBS [58,59].

Aside from being a candidate for personalized approaches, tES can be used easily in an outpatient setting, opening the door for home treatment approaches [56]. Furthermore, the various sources of individual variability may be identified if they are considered when designing a clinical study. To do this, a replication at the patient level would be required, through implementation of a repeated crossover design or with n-of-1 studies, which are multiple crossover studies conducted in a single patient [56].

A greater understanding of TMS and tES mechanisms, as well as the standardization of the main parameters are essential to achieve a clinically significant effect on pain reduction. To date, the majority of clinical studies have been phase II studies with small sample sizes and

[1] In a closed-loop configuration all TMS pulses are administered at a specific time, usually according to real-time electroencephalography (EEG). In this approach, rTMS is coupled with neuronal activities for a brain-state dependent stimulation [41].

small to moderate effects on pain levels. There is, therefore, a need for phase III pivotal studies with larger sample sizes [37].

Despite the motor cortex being the most used cortical target in chronic pain studies, the DLPFC (dorsolateral prefrontal cortex) seems to be a promising target [60,61], giving its efficacy in depression and the known link between depression and chronic pain [62]. The mechanisms from which the DLPFC is involved in pain regulation remain unclear. Although, this brain region is involved in several networks that could affect pain, such as the cognitive control network (through switching of default mode network and extrinsic mode network), the descending modulation of pain (enhancing activity in this network) and by reducing emotional/affective reactivity to pain through fear and reward circuitry [63]. The extrinsic mode network (EMN) is thought to be a generalized network that allocates cognitive resources to any cognitive task or sensory processing of the external milieu, whereas the default mode network (DMN) is active in the absence of any external task ("resting-state" or "task-negative" network) and is thought to be related to monitoring of the internal milieu and introspection [63].

Based on voxel-based morphometry studies, the most affected areas in chronic pain patients are the insula and the anterior cingulate cortex (ACC), showing a decreased volume. Various prefrontal regions (including the DLPFC) are also affected [64].

Hypothetical example of a clinical study with tES for chronic post-stroke pain

Only a fraction of stroke patients develops chronic post-stroke pain (CPSP), and this type of pain is thought to be caused by lesions in the somatosensory system [65]. A strengthening in the connections between the amygdala and the thalamus (in the unaffected hemisphere) also seems to contribute to the onset of the condition [66].

Stimulation of the motor cortex has demonstrated analgesic effects in some patients with CPSP [37,66]. However, the heterogeneity in pain conditions can be high since pain is a self-assessed condition. Therefore, to improve the number of patients who respond to treatment, an individualized approach should be considered, selecting patients who may respond better to stimulation [37].

The selection of patients with marked abnormalities in cortical networks involved in pain, as well as high levels of pain, may be a useful strategy for enhancing the effects of NIBS [37]. Also, the selection of patients based on similar multi-omics data (genomics, proteomics, metabolomics) and other parameters, such as age, health history, lifestyle and diet, and brain mapping could lead to the discovery of diagnostic, predictive or therapeutic biomarkers, improving the precision of NIBS in pain conditions [25].

At the intervention level, considering that in CPSP may be an interhemispheric imbalance, balanced bihemispheric stimulation could be used (anode in the injured hemisphere and cathode in the non-injured hemisphere) instead of the more common non-balanced bihemispheric stimulation, with the anode in the motor cortex of the injured hemisphere and the cathode in the supraorbital region [25]. A greater effect in pain reduction would be expected with simultaneous stimulation of the lesioned area and inhibition of the non-lesioned hemisphere, than with stimulation of only one hemisphere.

3.2. Case Study: Ethical and Regulatory Issues Associated with the Use of NIBS Devices

3.2.1. Do-it-yourself Brain Stimulation

Do-it-yourself (DIY) tDCS regards the home-use or the use of tDCS outside of the medical and/or academic setting, including the use of direct-to-consumer (DTC) devices and not just devices built/repurposed by individuals [67].

In late 2011, a Reddit community dedicated to tDCS-DIY was created (https://www.reddit.com/r/tDCS/), starting the DIY brain stimulation movement. By 2012, there were many blogs and websites devoted to the topic, suggesting that individuals' use of tDCS for both self-treatment and cognitive enhancement was increasing [67]. Some individuals built their own devices, while others purchased DTC devices or the cheaper tDCS kits (consisting of a battery, wires, electrodes, and a headband to ease electrode placement)[27]. Furthermore, some have purchased and modified iontophoresis devices, which deliver current levels similar to those used in tDCS but are not approved for the same purpose [27]. Currently, there is no Reddit community dedicated to DIY tACS; however, there is a growing number of posts about this “new” technology on r/tDCS. Also, several companies are selling DTC devices, either via their own websites, or via e-commerce platforms such as Amazon, eBay, or Caputron.com, which sells only neurostimulation devices [27].

In Wexler's (2018)[68] study of this online community, 43% of respondents said they use tDCS for treatment, with depression being the most frequent treatment indication. Wexler (2018)[68] also noted that individuals using tDCS for treatment reported this technique to be more effective, than those using it for cognitive enhancement. This may be due to tDCS being more effective for treatment than for cognitive enhancement, as some studies report greater effects on depression than on cognitive improvement [49]. Also, the effects of stimulation may be more prominent in individuals who use the technique for treatment, as a small increase in cognitive abilities may not be as noticeable. Moreover, tDCS may not be effective for either purpose, and then there is a greater placebo effect for those who use it for treatment [27].

Home users generally adhere to stimulation parameters used in scientific studies – current levels (1-2 mA) and length of stimulation sessions (20 min) [68,69]. However, they do not comply with the frequency of stimulation generally used (5 – 15 sessions), with some users taking more than 100 tDCS sessions [68].

According to Jwa (2015)[69] and Wexler (2018)[68], about 40% of home-users considered tDCS effective for the desired use – being treatment or cognitive enhancement. The side events reported on home users [68,69] are similar to those reported in literature and considered to be mild [49]. The risk of irreversible injuries is given by the use of at-home and unsupervised stimulation outside of controlled academic and/or clinical settings, because if the stimulation parameters are not properly chosen, it may result in maladaptive plasticity rather than beneficial effects [50].

Another use of tDCS that has been gaining attention is the practitioners who provide tDCS to clients in private clinics, outside of academic or clinical settings, and who may lack medical training and provide tDCS for indications for which there is little evidence [27].

Some academics have claimed that there is a regulatory gap for consumer cognitive enhancement devices due to the variety of marketing techniques and the lack of enforcement action. However, a lack of enforcement action should not be confused with a lack of regulation since both medical devices and consumer items are subject to a thorough regulatory system (both in the USA and in the EU).

In the EU, the MDD covered only medical devices with a medical purpose [3]. Some tES manufacturers took advantage of that by not claiming any therapeutic indications for their devices, allowing them to market these products without any oversight. The only applicable legislation was the General Product Safety Directive (GPSD - Directive 2001/95/EC), that considers a "product" as "any product that is intended for consumers and is supplied or made available in the course of a commercial activity (Article 2(a) of the GPSD) [70]. The GPSD is only fully applicable when a product is not covered by other specific community legislation. When specific legislation exists, as in the case of medical devices, the GPSD only applies to the aspects not covered by such legislation (Article 1(2) of the GPSD) [70].

Currently, the MDR covers devices both with and without a medical purpose when they are based on a similar technology [1]. Devices without a medical purpose are addressed in Annex XVI, which includes "equipment intended for brain stimulation that apply electrical currents or magnetic or electromagnetic fields that penetrate the cranium to modify neuronal activity in the brain" [1]. This new legislation guarantees that devices marketed for a non-medical purpose will need to comply with certain MDR requirements, such as risk management plan (Article 1(2) of the MDR) and comply with relevant CS adopted by the Commission for those products (Article 9(4)).

In the USA, devices with a non-medical purpose are not under FDA (Food and Drug Administration) jurisdiction so, new companies continue to bring tDCS devices that claim to improve memory, mood or cognition to the market [27]. Also, since these devices are considered low-risk products and are marketed for general wellness, FDA does not intend to regulate them [27].

In the EU, the practice of medicine is regulated by individual member states. In the US, state laws regulate who can prescribe drugs, but there are no similar restrictions for the use of medical devices – no licensing is needed to use medical devices on individuals in a medical setting [27]. As a result, practitioners are free to use any device, whether FDA-approved and used for the intended indication, FDA-approved but used off-label, or even not FDA-approved devices.

In the context of NIBS, the main ethical issues are safety (relating to the bioethical principle of nonmaleficence and beneficence), coercion and peer pressure (relating to the principle of autonomy: informed consent and identity/personhood) and justice (fairness and equity) [27,71].

Safety comprises both the side-effects/adverse events and the unknown cognitive effects of neurostimulation. Among the 18000 individuals who underwent tES, no SAEs were

observed, only mild adverse events (like tingling, headaches and burning sensations) [72]. Even though the literature has not identified any serious side-effects of NIBS, a group of scholars has written an open letter regarding DIY users of tDCS [73].

Wurzman et al. (2016) [73] highlighted the unknown risks of NIBS, including the interaction of stimulation with ongoing brain activity (state-dependency) and the fact that the enhancement of cognitive skills may come at the cost of others (as pointed out by Brem et al. (2014) [74], neuroenhancement may be a net zero-sum proposition, implying that neural "gains" are balanced by "neural losses"). Moreover, changes in brain activity may last longer than a user thinks, and small changes in parameters (intensity, electrode placement, duration) may have unpredictable effects.

Coercion may also be an ethical concern related to the use of NIBS in educational, military, or occupational contexts, either via social pressure or through regulations and policies. However, coercion may only be a real problem if these technologies prove to be effective and become widespread [27,68].

Regarding distributive justice, as with coercion, it will only be an issue if these technologies demonstrate effectiveness and widespread social use. A disproportionate use by higher socio-economic classes may exacerbate inequality [27]. In Wexler's (2018) study, individuals who use DIY-tDCS have relatively high incomes [68].

tDCS home-users generally cooperate, exchanging and discussing scientific papers, and creating derivative work, including websites with electrode-placement diagrams in an easy to understand format [67].

The challenge for this field is to create policies that tackle the problems arising from the use of NIBS at home, such as the improper placement of electrodes, the fact that reversing polarity might impair cognitive function, the unknown long-term effects, and the potential interaction with concomitant medication [75].

One apparent issue is that of left-handed people, whose brains may be structured differently than those of right-handed people [76]. It is also likely that small variations in subject's neuroanatomy might change the effects [75].

Those writing about tDCS should recognize that their readership reaches beyond scientists and their choice of words may have unexpected consequences. For example, it is important to note that the term "non-invasive" refers to a procedure that does not require an incision or insertion in the body. However, for a lay person, the term "non-invasive" may mask the possibility of side events and long-term effects of neurostimulation [75].

Some NIBS devices (those without a health claim) are being marketed without clear information about the risks and mechanisms of action. That said, some scholars suggest that a policy for the home use of these technologies is required along with indications on its specific protocol and potential risks [77]. Also, clear guidelines are still needed on standard tDCS application protocols (and other NIBS), which include parameters such as electrode placement, length of stimulation, intensity, and number of sessions. To avoid this excessive use (both in length of stimulation and number of sessions) and therefore to guarantee safety, devices marketed for home-use, or the ones used in home-based NIBS studies

should contain a block system. There should also be a periodic safety remote monitoring of the device, enabling the detection of a possible device malfunctioning.

3.2.2. Neuroenhancement (and Neurodoping)

Neuroenhancement refers to the use of neurotechnologies or medicinal products in healthy individuals to increase basic brain functions, such as memory, perception, attention, conceptualization and motor performance [72,78].

Neurodoping (or brain doping) can be defined as the use of brain stimulation techniques to increase athletes' performance [79]. Although, some scholars define it more broadly, referring to the use of drugs and methods that are believed to improve mental capacities in order to enhance athletic performance[80].

The benefit of NIBS for neuroenhancement (and neurodoping) is still unknown as the existing literature contains a mix of findings. Systematic reviews and meta-analyses indicate either a small positive effect [81–83] or no effect at all [84]. tDCS may increase creative thinking and memory and minimize tremors, allowing athletes to remain steady throughout or before competitions in sports like pistol shooting [85]. These potential effects of tDCS are comparable to those of amphetamines, which improve memory and attention, and beta-blockers, which minimize tremors [85]. Both drug classes are on the World Anti-Doping Agency's (WADA) list of banned substances [86]. Also, Angius et al. (2017)[87] claims that tDCS may have a favorable effect on exercise ability and the company Halo Sport ensures their device has ergogenic benefits and can help athletes improve their performance [88].

Davis (2013)[89] claims that NIBS will possibly have little effect on the performance of elite athletes, who already push the human body to its physical limits, since most studies recruit non-expert healthy subjects and assess performance in conditions where it is expected to change but not to reach its peak.

On the contrary, according to Montenegro et al. [90], tDCS may have physiological benefits in highly fit individuals but not in non-trained ones. Anodal tDCS administered to the left temporal lobe at rest may have physiological benefits, increasing heart rate variability in highly trained participants, enhancing the parasympathetic heart rate regulation, and reducing the sympathetic one.

Since the existing research does not support a great efficacy of tDCS in cognitive and sports enhancement, making claims about these advantages of NIBS and/or its prospective use as a novel doping technique seems premature and misleading.

Given that the enhancement may apply only to some people, because of inter-individual variability, ethical issues may be raised, mainly related to fairness. The use of NIBS in healthy individuals may exacerbate existing inequalities, or possibly create new ones, placing certain people at a disadvantage[91].

Specific properties of NIBS appear to imply important ethical issues:

1. The already mentioned unlimited and unrestricted self-administration. In contrast, with some exceptions, chemical enhancer availability is always dependent on others [91];

2. The variability in intra- and inter-subject responses to stimulation. Inter-individual variability may lead to problems of equality of opportunity, given that the different responses to NIBS are linked to characteristics that people cannot change, such as skull thickness, subcutaneous fat levels and cerebrospinal fluid density [91,92];

3. The use of NIBS on healthy individuals for cognitive (or athletic) enhancement is currently undetectable, which makes it almost impossible to impose restrictions on the use of NIBS, except in specific circumstances (e.g., monitoring athletes long before a race) [91].

These three aspects contribute to the complexity of NIBS' issues, showing the need for a comprehensive and well-defined framework. Another important issue to consider is safety. However, this issue has been already discussed in the previous section.

The use of tDCS to improve athletic performance has gained a lot of interest, since it has been revealed that certain athletes who competed in the 2016 Olympic Games in Rio de Janeiro were also trained with tDCS to stimulate the motor cortex [91,93].

Some scholars argue that sports outcomes should be dependent on the individual athlete's abilities and decision-making, and for sport to be meaningful, winning should indicate better athletic skills [79]. Others have suggested that the use of neurodoping like tDCS and cognitive boosting medications such as *Ritalin*® or *modafinil* by healthy athletes should be prohibited [85]. Arguments for this point of view include concerns about neurodoping's harmful health consequences on athletes, its incompatibility with the "spirit of sport[2]", or societal pressure on athletes to use doping if it is not prohibited [80]. Also, even if legalization of neurodoping would not result in any of these concerns, the fairness objection may be a compelling reason to prohibit its usage.

The numerous means of tDCS' enhancement with its unforeseen safety issues, and the fact that it is still in an experimental phase will certainly continue to be a source of ethical concerns. As a result, anti-doping authorities should be proactive in amending or reinforcing rules that instruct athletes, athlete supporters, and law enforcers in terms of the legitimacy of NIBS approaches [85].

The equality of opportunity appears to be fundamental to the idea of sports competitions. Thus, enabling athletes to use neurodoping may exacerbate the already existing socioeconomic inequity among them, given that wealthy athletes already have privileged access to more expensive performance-enhancing devices. Although, this might not be an issue if there are no health concerns associated with neurodoping and if equal opportunities exist [80].

Neurostimulation methods are not currently prohibited by the World Anti-Doping Agency (WADA). However**,** WADA has a program to monitor the usage of drugs that are not on the

[2] According to WADA, the spirit of sport is reflected in values we find in and through sport, such as dedication and commitment, respect for rules and laws and for self and others, courage, solidarity, ethics, fair-play and honesty, health, teamwork, and excellence in performance [94].

banned list, but that the agency wants to monitor to discover trends of misuse. Caffeine is one of the substances in this list [86], although there is evidence of its performance-enhancing impact. It was removed from the prohibited list in 2003, owing to problems in differentiating performance-enhancing dosages from regular everyday intake of coffee and soft drinks [95].

One way to deal with the uncertainty regarding NIBS safety and effectiveness in sports performance is to include these techniques in the WADA's monitoring program. Also, as part of that monitoring, WADA could collaborate with companies that develop tDCS devices, to guarantee that athletes are informed about the effects and risks of brain stimulation [95].

3.2.3. Marketing to Vulnerable Populations

A vulnerable group or population refers to those who are susceptible to harm by others. The freedom and ability of vulnerable people to defend themselves against intentional or inherent risks may be limited, ranging from decreased free will to the inability to make rational and informed decisions [96].

For the scope of this report, the youth, the mentally ill and elderly are considered to be vulnerable groups. The marketing of products, or in this case, neurotechnology devices, to the vulnerable groups in ways that may take advantage of their vulnerability is unfair and morally wrong. It is still uncertain if DTC NIBS devices perform as marketed – to ameliorate neuropsychiatric disorders' symptoms and/or to enhance cognition. Companies, like Flow Neuroscience, have undertaken little to no research on their products' effectiveness [97], and some depend entirely on studies conducted in laboratory settings using research-grade medical devices [27]. Additionally, as previously stated, the scientific literature on the effects of tDCS is conflicting. Given the difficulty of consumers, and particularly consumers from a vulnerable group, to evaluate the authenticity of claims made by DTC neurotechnology companies, more caution should be taken by these companies in ensuring that their claims are factual and compatible with the scientific research [97].

The ethics and risks associated with NIBS are barely covered in the media, with these neurotechnologies receiving only a positive coverage [98]. Misinformation and inaccurate reporting are common in neurotechnologies, favoring simplification [98]. An assessment and discussion in the media about the potential ethical and social issues raised by neurotechnologies (including NIBS) is important, as they may mislead individuals into enrolling in experimental studies for the wrong motives or convince vulnerable groups into buying products that are far from what the companies promise [98].

4. Curricular Internship in a CTU

4.1. Vision of the Host Institution

The curricular internship was performed in the CRU^{2}C, the Clinical Research Unit University of Coimbra, that is anchored in the Institute of Nuclear Sciences Applied to Health (ICNAS). In the following paragraphs, it will be provided a brief description about the ICNAS, and more specifically about the clinical research unit, its services, and main objectives.

The ICNAS is an organic unit of the University of Coimbra. It is involved in various national and international projects, ranging from basic nuclear physics to clinical development.

CRU^{2}C is the Clinical Trial Unit (CTU) of the University of Coimbra (UC). It is an academic venture between ICNAS, ICNAS-Produção and the Laboratory for Biostatistics and Medical Informatics of the Faculty of Medicine of University of Coimbra (LBIM).

Besides being anchored in the ICNAS, the CTU is also anchored in the CIBIT, the Coimbra Institute for Biomedical Imaging and Translational Research, a R&D unit of the UC with expertise in Cognitive, Translational and Clinical Neuroscience.

The CTU's mission is to provide information, guidance, and representation to investigators in order to successfully reach high quality, efficient and sustainable Investigator Initiated Trials (IITs), compliant with the ICH-GCP guidelines. CRU^{2}C offers non-for-profit rates expertise to support all stages of clinical research, according to the requirements of ethics and regulatory authorities. The activities of CRU^{2}C range from protocol design and authorities' approvals to final analysis and outcomes reporting.

CRU^{2}C is a member of the Portuguese Clinical Research Infrastructure Network (PtCRIN), the Portuguese node of the European Clinical Research Infrastructure Network (ECRIN), and is currently involved in over a dozen IITs, being some of them multinational trials.

4.2. Internship objectives

The main goal of my curricular internship was to apply and consolidate the knowledge acquired during the teaching component of the Master's Course in Clinical Research Management. More specifically, the goals set for this internship were:

- To understand and acquire experience on the regulatory process guiding clinical trials and clinical studies with medical devices and to know and be able to interpret the main provisions of the new EU regulations (Clinical Trials Regulation and MDR/IVDR);
- To understand the role of the different members of a CTU;
- To identify areas of interest within the clinical research field;
- To recognize the challenges inherent to a clinical study development;
- To improve my writing skills;
- To gain and improve personal and soft skills (autonomy, resilience, self-confidence, communication, problem-solving and critical thinking).

4.3. Activities carried out during the internship

4.3.1. Preparation of the submission dossier for requesting an ethics opinion from CEIC

One of the activities proposed during the internship was the preparation of some documents of the dossier for a phase II investigator-initiated trial with a radiopharmaceutical in the area of neuro-oncology.

The preparation of the submission dossier for requesting a national ethics committee opinion for the conduct of a clinical trial must comply with the structure defined by CEIC (Figure 4).

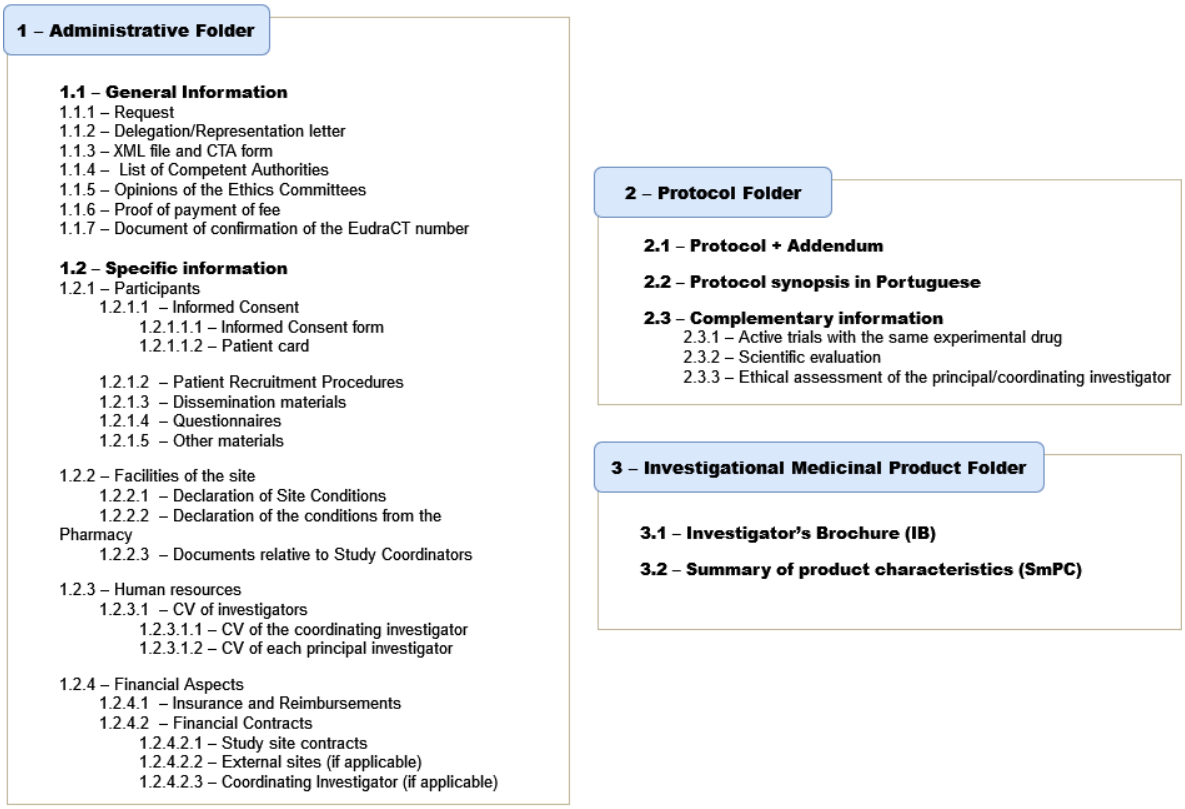

Figure 4 - Structure of the submission dossier for requesting an opinion from CEIC.

As shown in the figure, the documentation must be organized in three folders: the Administrative Folder, the Protocol folder, and the IMP (Investigational Medicinal Product) Folder. If there is a need to submit additional files, other folders can be added.

In this activity I had the opportunity to develop the following documents:

- **List of Competent Authorities:** a document in which are presented the competent authorities of the Member States to which the application for authorization has been submitted.

- **Opinions of the Ethics Committees**: this document presents all the opinions of the ethics committees of the Member States involved, to which the request for an ethics opinion has been submitted.
- **Patient Recruitment Procedures:** a document in which the participant recruitment strategies outlined for the study are described.
- **Dissemination Material:** the CEIC considers that the dissemination of clinical trials must be directed to the general population and appropriate to the age group/study population and carried out in specific locations (such as health units and patient associations). The dissemination material must contain the title of the study, the pathology under study and the objective of the trial, a summary of the inclusion and exclusion criteria, the treatment groups, a summary of the potential risks of SAEs, the recruitment and study duration, and the identification of the study sites and their contacts.
- **Declaration of Site Conditions:** a statement that indicates that every department of the study site have the necessary equipment, facilities, and human resources.
- **Declaration of the conditions from the Pharmacy:** a document in which the head of the pharmacy services states that the department has appropriate conditions to carry out all IMP-related activities.
- **Declaration of Compensation/reimbursement of Research Participants:** statement in which the Coordinating Investigator and/or Principal Investigator guarantees that research participants will not be paid for their participation, according to the applicable law. They will only be reimbursed for expenses caused by participation, such as travel expenses to the study site and wage losses.

In addition to the preparation of these documents, the reading of this research project allowed to deepen my knowledge of glioblastoma multiforme (GBM), namely its pathogenesis, the approved treatments and standard-of-care, the survival time of patients, and theranostics.

The term theranostics refers to the combination of diagnostics and therapeutics in the individualized management of disease [99]. To obtain diagnostic images as well as to administer a therapeutic radiation dose to target tissues, theranostics uses molecular targeting vectors (e.g., receptor binding particles and monoclonal antibodies) labeled with radionuclides. This can be done by incorporating two radionuclides (one for imaging and the other for therapy) into the same theranostics radiopharmaceutical, or by using one radionuclide that emits both therapeutic (α or β^-) and diagnostic (γ or positron) radiations [100].

Contrary to the Clinical Trials Directive, the new CTR (Clinical Trials Regulation – 536/2014) recognizes specific requirements for diagnostic radiopharmaceuticals (as therapeutic radiopharmaceuticals are considered in the same way as other medicinal products). The CTR introduces that for diagnostic radiopharmaceuticals the manufacturing and import authorization will no longer be needed, where this process is carried out in hospitals, health centers or clinics (Article 61(5) of the CTR), which makes it easier to prepare these radiopharmaceuticals to be used as IMPs in clinical trials [101]. There is also no need for GMP (Good Manufacturing Practice) production of diagnostic radiopharmaceuticals used

as IMPs and prepared and used in hospitals, health centers or clinics (Article 63(2) of the CTR), and the labelling of diagnostic radiopharmaceuticals used as IMPs and AMPs (Auxiliary Medicinal Products) is now simplified (Article 68) [101].

4.3.2. CTIS – Clinical Trials Information System

During the internship I was also able to learn how to use the future Clinical Trials Information System (CTIS) from the perspective of small and medium enterprises (SMEs) and academia.

The CTIS introduced by the Clinical Trials Regulation (CTR – Regulation 536/2014) will allow all clinical trial applications (CTA) to be submitted through a single portal, simplifying and speeding up the application process. The portal will also function as a communication platform between sponsors, MS, the EC and MAH (Market Authorization Holder). The European Medicines Agency (EMA), in cooperation with the Member States and the European Commission, shall establish and maintain this system (Articles 80 and 81 of the CTR) [101].

To help SMEs and academia prepare for the use of CTIS, the EMA created a training programme, consisting of a webinar divided in two parts.

The first part covered:

- Overview of CTIS
- User access management and ‘how to register users’
- Sponsor user management
- Sponsor roles and permissions

The second part covered:

- Submitting an initial trial application in CTIS
- Updating an initial trial application, including making substantial modifications and adding a Member State concerned
- Making non-substantial modifications
- Submitting trial results

Overview of CTIS

The CTR is in force since 2014 but its application is dependent on the full functionality of the CTIS. The CTIS is planned to go live by 31 January 2022 [102]. Currently, CTs are being recorded in the EudraCT database. There will be a 3-year transition period from the Clinical Trials Directive to the CTR. During the first year of application of the CTR, sponsors will have the option of submitting CTAs under the Directive or the CTR. From the second year, initial CTAs will need to be submitted under the CTR. However, CTs authorized under the Directive will remain under that regime until the third year of application of the CTR. From the end of the third year of implementation, all clinical trials (including ongoing trials submitted to EudraCT) will have to be migrated to the CTIS [102].

CTIS is composed of three virtual landscapes: a sponsor workspace, an authority workspace and a public portal. The public portal will work similarly to the US clinicaltrials.gov, providing patients, healthcare professionals and the general public with searchable clinical trial information, presented in a technical and lay language.

The sponsor workspace will assist sponsors in the submission and update of the CTA dossier to the system for the assessment by Member States. It will also cover the submission of events happening during the trial life cycle (e.g., withdrawal, start of trial, end of recruitment, end of trial, early termination, serious breaches, unexpected events), the submission of clinical study report summary and the submission of inspection reports of third country authorities.

The authority workspace will support the activities of Member States and the EC in assessing, authorising, and overseeing clinical trials. Member States will be able to view CTA dossiers, collaborate with other MS, receive alerts and notifications for ongoing trials, download documents submitted by the sponsors and record inspections of sites and CTs.

Both sponsors and authorities have access to four common functionalities: overview of clinical trials, notices & alerts, user management, and annual safety reporting. “Overview of clinical trials” will allow users to search, select and view a clinical trial, and to monitor the status and information of clinical trials stored in CTIS. “Notices & alerts” will allow users to monitor the messages triggered by events that have occurred during the lifecycle of a clinical trial in which they are involved. “User management” will allow users with an administrator role to manage the roles & permissions of registered users that belong to their organization or Member State. “Annual safety reporting” will allow sponsors to submit the annual report on the safety status of their trials, and to have them assessed by Member States.

User access management and ‘how to register users’

All users (Sponsors and Member States) will have to self-register in the EMA Identity and Access Management system (IAM) to get access to CTIS. Users will receive with their log in credentials a default role that will allow them to access CTIS and to request a role, update personal profile and create a CTA via the centric approach (but only if there is no sponsor administrator registered for the organization the user selects for that particular trial). In order to perform additional CT (Clinical Trial) related actions, users need to be assigned with business roles by the user administrators.

Sponsor user management

User management refers to a set of capabilities that allow CTIS administrators to manage user access to CTs through role assignment while also allowing each user to manage their own roles and profiles. CTIS roles can only be assigned to users who have previously self-registered in the EMA IAM system.

The CTIS User Management is structured in a hierarchical manner. The administrator roles (Sponsors, MS, EC, EMA) are responsible for managing users via the user management functionality. CTIS allows for more than one user administrator per organization or per CT.

Users will have access to the CT system functionalities according to their role, with the system presenting the necessary data and the appropriate activities for them.

User Management also enables users to manage their roles, including the ability to view, request (only in the sponsor workspace), amend role/provide access to CTs, and to manage user profile (personal details and employer information).

The high-level administrators (Sponsors, MS) will be assigned in the IAM system. In that process they will need to be validated. For that, the sponsor will be required to provide certain documentation for the sponsor administrators to be validated. These high-level administrators will be able to assign direct roles to business users (CT coordinator, viewers, preparers, submitters) or instead they can assign roles to medium-level administrators (Clinical Trial Administrator).

There are different user management approaches that are relevant for the Sponsor users' group: the Organisation-centric approach and the Trial-centric approach [103]. The Organisation-centric approach is expected to be used by all the commercial sponsors. In this approach all the users will be handled at an organization level by the high-level administrator and will have access to all trials under the umbrella of their organization [103]. The Trial-centric approach is only available in the sponsor workspace. It is a bottom-up approach, in the sense that a user registers and automatically can create a CTA. The difference is when they choose a sponsor organization, the system will verify if the organization already has a sponsor administrator. If the organization does not have a sponsor administrator, the user can proceed and will be able to create the initial CTA. In that moment, the user will automatically become the CT administrator for that CT. This trial-centric approach has been created in CTIS to facilitate the conduct of CTs by non-commercial sponsors (academia), supposing there will not be many CTAs from their side [103]. This approach allows a faster process in case of a first initial application because it does not require the validation of the sponsor administrator by the EMA [103]. On the other hand, this approach can lead more easily to duplicate sponsor data and is less convenient if the organization applies for multiple CTs.

Sponsor roles and permissions

The roles-permission matrix in CTIS provides a flexible system that lets us adjust the roles. A role can be defined as a job function with a set of permissions, such as Sponsor administrator, CT administrator, viewer, preparer, submitter.

A permission is an approval to do something. The role matrix is made up of a set of predefined permissions: create, view, delete, share, submit, assign/release task, assign roles/trials, withdrawal and update.

The difference between the sponsor administrator and the CT administrator is that the sponsor administrator can manage all users under the umbrella of their organization whereas the CT administrator only can administer business roles in all or specific trials (depending if they are CT admin for all trials). The sponsor admin is purely an administrator and cannot perform business activities in the system (Figure 5).

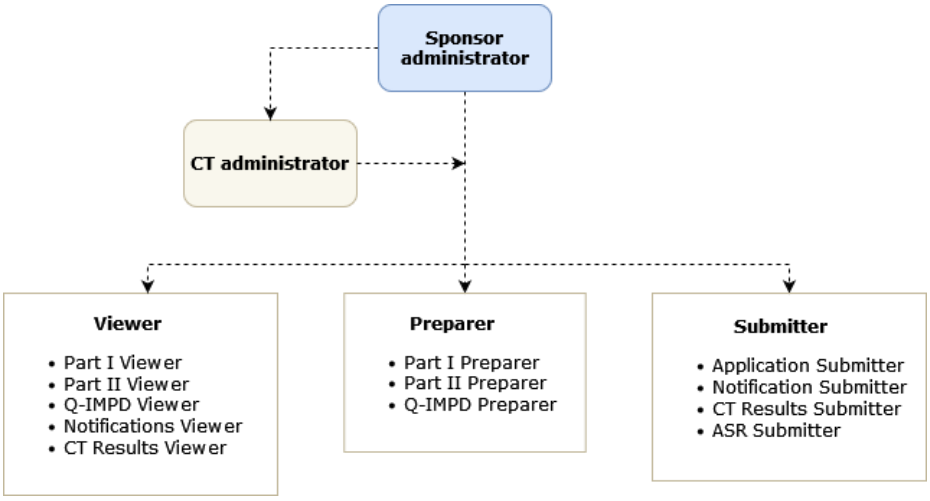

Figure 5 - Sponsor workspace roles: sponsor administrator and CT administrator, and business roles (viewer, preparer, submitter). Q-IMPD – Quality part of the Investigational Medicinal Product Dossier.

Submitting an initial trial application in CTIS

CTIS supports sponsor users in the compilation, submission and reporting on data of CTs carried out in the EU. The CTR introduced a harmonized procedure for the submission of CTAs. There are three types of applications: initial CTA, substantial modification (SM) CTA and Additional MSC CTA.

The initial CTA is the application that provides comprehensive information about the CT to be conducted (including information of the CT subjects and specific information for each MSC) and the investigational medicinal product(s) to be used, enabling the authorities of the MSCs to evaluate the acceptability of conducting the CT. Initial CTAs can involve one MSC (mononational) or more than one MSC (multinational).

In the Initial CTA page four sections are displayed: Form, MSC, Part I, and Part II. The content of the application dossier for an initial CTA is specified in Annex I of the CTR. When submitting an initial CTA, sponsors have the option to submit a full dossier (Part I and II) in accordance with Article 5 of the CTR, or submit a partial application with Part I only, or submit Part I and II for some of the MSC (Article 11 of the CTR) [101]. When submitting a partial application with Part I only, the sponsor has two years to apply for an authorization to Part II.

In the Form section, users upload documents and general information about the CT such as the cover letter, the proof of payment of the fee in the various MSCs, and the anticipated publication dates of the CT information.

In the MSC section, users specify the MSCs for the trial they intend to conduct and the number of subjects to be recruited in each of them. For multinational CTA, users need to select a proposed RMS (Reporting Member-State). Also, this section displays countries outside the EEA where the trial is to be conducted.

In Part I, users need to upload scientific CT-specific information such as protocol information, CT design, inclusion and exclusion criteria, conditions to be treated, the

therapeutic area, the Investigator Brochure, the Investigational product dossier, countries outside the EEA where the trial is to be conducted.

In Part II, users upload regulatory data and documents, such as the informed consent form and procedure, subject recruitment arrangements, suitability of the investigator, suitability of the facilities, the trial sites. Information of this sections must be provided for each MSC where the trial is to be conducted, as it is MSC specific information.

Two additional sections, the Evaluation and the Timetable, will display information regarding the evaluation of the CTA, after the submission.

The resubmission of a CTA is facilitated in the CTIS since there is a Copy button and the possibility to select the information the sponsor user wants to copy.

Updating an initial trial application, including making substantial modifications and adding a Member State concerned

An Additional MSC application simply refers to a request by the sponsor for extending an authorized CT to another MSC (Article 14 of the CTR) [101]. A sponsor can submit an additional MSC application when there are no other applications under evaluation, but also if there are other additional MSC applications under evaluation and if there is an assessment for a substantial modification part II ongoing in other MSC. When submitting this application, the CTIS requires sponsors to populate some fields, such as the estimated number of subjects to be recruited in each MSC, the trial site details and other Part II mandatory documents.

The Substantial Modification (SM) is the application submitted after the notification of a decision on a CTA, related to any change of the CT likely to have a substantial impact on the safety or rights of the subjects, or on the reliability and robustness of the data generated (e.g., change in the definition of the end of the trial, new insurance policy, amendment of the number of subjects included). The application dossier for a SM is covered in Annex II of the CTR [101].

There are three types of SMs: SM of Part I, SM of Part II and SM of Part I and II. Furthermore, SMs can also be divided in single-trial SM and multi-trial SM, depending on the number of trials the sponsor wants to apply a SM for [104].

Making non-substantial modifications

During an ongoing CT, sponsors can also perform non-substantial modifications (that are not considered as applications since they are not evaluated by the MSCs).

A non-substantial modification is a change made to a CT with the purpose of rectifying information, that is not likely to have a significant impact on the safety or rights of subjects or on the reliability and robustness of the data generated in the CT (e.g., correction of typographical errors, and administrative changes, such as the update of contact details) (Article 81(9) of the CTR).

Non-substantial modifications should not be submitted during the RFI (request for information) phase of an ongoing assessment unless they are requested as part of the RFI response.

Submitting trial results

According to Article 37(4) of the CTR, the sponsor must submit to CTIS a summary of the results of the trial, regardless of the outcome, within one year from the end of a clinical trial in all Member States concerned or within six months for a trial in pediatric population. This summary of results shall be accompanied by a summary for laypersons, which content is set out in Annex IV and V of the CTR, respectively [101].

While the sponsors are required to provide a summary of results and a layperson summary after the completion of each trial, the MAH is required to submit the Clinical Study Report (CSR) if the clinical trial was intended to be used for obtaining a marketing authorization for the IMP.

The CSR describes the outcomes of the clinical trials carried out in the EU and/or third countries, providing details on how the data were collected and analyzed, and must be submitted within 30 days after the day the marketing authorization has been granted, the procedure for granting the marketing authorization has been completed, or the applicant for marketing authorization has withdrawn the application [104].

The CSR includes a title, a synopsis, a table of contents for the CSR, a list of abbreviations and definitions of terms, the ethics of the clinical study, the investigators and study administrative structure, the study objectives, the investigational plan, the study patients, the efficacy evaluation, and the safety evaluation [104].

4.3.3. Pilot project for the submission of CTA

To facilitate the implementation of the CTR in Portugal, the CEIC and the Infarmed developed a pilot project of the national Coordinated Assessment Procedure between both entities, similar to what will happen when the CTIS becomes operational [105]. During the internship I had the opportunity to gain knowledge on the submission procedures and submission dossier of this project.

This pilot project, of voluntary participation, aims to give sponsors and the competent authorities involved (Infarmed and CEIC) the possibility to prepare for the new procedures and timelines for assessment of initial clinical trial applications (CTAs) and to make the necessary adjustments before the entry into application of the Regulation [105].

The project applies only to initial CTAs and does not cover applications for substantial modifications, nor clinical trials with advanced therapeutic medicinal products (ATMP), with genetically modified organisms (GMOs), first-in-human (FIH), emergency trials, clinical trials for a COVID-19 indication, and low-intervention clinical trials [105].

The Infarmed, as the National Competent Authority (NCA), will serve as contact point with the applicant. The applicant/sponsor should only interact with the CEIC in case of a RFI [105].

Submission procedures:

1. At least 14 days before the planned submission date, the applicant sends a letter of intent to Infarmed (ensaios.clinicos@infarmed.pt). In this letter (model available at Infarmed's website), the applicant commits, if the CTA is accepted in the pilot project, to formal submission via RNEC and payment of the applicable fee in line with Ordinance no. 63/2015, upon completion of the assessment, regardless of the positive or negative outcome of the assessment.
2. Within 10 days, Infarmed will inform the applicant whether the CTA may be included in the pilot project. If participation is confirmed, the applicant sends the complete CTA (according to the Annex I of the CTR, and in structured folders – Table 2) to ensaios.clinicos@infarmed.pt.
3. Infarmed will inform the applicant of the outcome of the validation within 10 days (includes validation of CEIC exclusive documentation).
4. If the application is not valid in the initial submission, Infarmed (after liaising with CEIC) will send a request for elements to the applicant. The applicant is requested to respond within 10 days to Infarmed, who validates the supplementary documentation (in articulation with CEIC, if applicable) within 5 days of receipt.
5. If the application is valid, it will be assessed by Infarmed and CEIC at the same time.
6. If required, the applicant will receive a RFI/Questions (grounds for non-acceptance, GNAs) within 26 days of receipt of the notification of valid application. RFIs/GNAs regarding Part I of the dossier will be sent by Infarmed (including CEIC questions, when applicable), via email. RFI/GNAs for Part II of the dossier will be sent by CEIC. RFI/GNAs from both entities will be sent to the applicant on the same day. The applicant should respond to the RFI/GNAs within 12 days to Infarmed and/or CEIC.
7. The entities evaluate the response within 12 days and conclude on the evaluation. The applicant will receive the decision via email.
8. Upon receipt of the decision on the application submitted under the pilot, the applicant will have to submit the CTA through RNEC to Infarmed and CEIC following the current guidelines (Law no. 21/2014). Having the documents been assessed during the pilot process, the final decisions of Infarmed and CEIC will be taken and communicated in RNEC within 5 days, provided the applicant ensures that the documentation submitted is the same as the documentation previously assessed in the pilot project (through a declaration of commitment that must be part of the submission documentation via RNEC).

Table 2 - Structure of folders (Part I and II) defined by Infarmed and CEIC for the submission of an initial CTA, for the coordinated assessment procedure pilot project [105].

Annex I of the CTR	Documents	References/Instructions
PART I		
A – Introduction and General Principles	-Referral to previous applications/ different sponsor agreement; -Responsibility of each of the sponsors (if more than one); -Signature of the sponsor/representative of the sponsor.	The section may be left blank if no specific information is available.
B – Cover letter	-Signed request.	Shall include EudraCT no., protocol no., draw attention to any features which are particular to the clinical trial, location of the reference safety information (RSI). It is not necessary to reproduce information that is already in the application form, except for paragraph 7 a) to i) of Annex I.
C – EU Application Form	-The application form dated and signed, in pdf and in XML format.	The EudraCT form as the CTR EU form is not yet available.
D – Protocol	-Protocol.	In compliance with ICH E6 GCP. Accompanied by a synopsis in PT and EN, and the Charter of the Data Safety Monitoring Committee, if applicable.
E – Investigator's Brochure (IB)	-Investigator's Brochure or the summary of product characteristics (SmPC).	IB in compliance with ICH E6 GCP.
F – Documentation relating to compliance with Good Manufacturing Practice (GMP) for the Investigational Medicinal Product	-Copy of manufacturing/ import authorization -Declaration by the qualified person (QP) in the Union that the manufacturing complies with GMP in the Union.	
G – Investigational Medicinal Product Dossier (IMPD)	-Full or simplified dossier of the Investigational Medicinal Product(s)	Data presented in the ICH-CTD structure (Modules 3,4 and 5). A statement of the Good Laboratory Practice (GLP) status. The details of the simplified IMPD are set out in paragraphs 50 to 54 of the Annex I.
H – Auxiliary Medicinal Product Dossier	-Auxiliary Medicinal Product Dossier or SmPC.	
I – Scientific Advice and Paediatric Investigation Plan (PIP)	-Copy of the summary of scientific advice of the EMA, or of any Member State or third country	

	and/or -Copy of the EMA decision on the agreement on the PIP, and the Paedriatic Committee opinion (or link to this documentation in the cover letter).	
J – Content of the Labelling of the Investigational Medicinal Products	-Labels.	Example of draft IMP labelling in accordance with Annex VI of the CTR [101].
PART II		
K – Recruitment Arrangements	- Procedures for inclusion of subjects and a clear indication of what the first act of recruitment is.	A separate document or the reference to the relevant section of the protocol.
	-Copy of the advertising materials.	In a folder separate from the protocol. Shall comply with CEIC's Guiding Document on Clinical Trial Dissemination: "Considerações CEIC sobre a Divulgação de Ensaios Clínicos: Princípios Orientadores".
L – Subject Information, Informed Consent Form and Informed Consent Procedure	-Informed Consent Form -Questionnaires -Subject Card -Diaries -Other documents for the subject -Informed Consent Procedure.	Must be submitted according to the folder structure. The Assent/Consent must comply with the CEIC's Guiding Document: "Consentimento Informado (CI) para participação em ensaios clínicos em pediatria" if applicable.
M – Suitability of the Investigator	-CV of the Principal Investigator(s) -Training in GCP -Statement of interests of the investigator.	
N – Suitability of the Facilities	-A duly justified statement on the suitability of the study sites in terms of facilities, equipment, and human resources.	A declaration from the head of the site or other responsible person indicating the equipment, infrastructure, and identification of all the members of the research team and involvement of the institution's pharmaceutical services, as well as a declaration of the pharmaceutical services, and the medicinal product circuit (CEIC's Guiding Document: "Circuito dos produtos medicinais investigacionais e auxiliares em ensaio clínico").
O – Proof of Insurance Cover or Indemnification	-Proof of insurance, a guarantee, or a similar agreement.	In compliance with paragraph 68 of Annex I [101] and with Law No. 21/2014 [7].

P – Financial and Other Arrangements	-Financial agreement between the sponsor and study sites -Financial transactions and compensation paid to subjects and investigators for participating in the clinical trial -Any other agreements between the sponsor and study sites.	In compliance with Annex I ("Informação a constar nos Contratos Financeiros e cujos elementos integram o pedido de avaliação do Ensaio Clínico") of the document "Projeto Piloto de Submissão de Ensaios Clínicos de acordo com o Regulamento (UE) n.º 536/2014, de 16 de abril".
Q – Proof of payment of fee – Not applicable in the pilot project		
R – Proof that data will be processed in compliance with union law on data protection	-Statement by the sponsor or its legal representative	A document in which the sponsor, or its legal representative, declares that data will be collected and processed in compliance with the applicable legislation on data protection (GDPR).

4.3.4. Regulatory Framework of TMS

Another activity proposed to me was to research the regulatory framework of transcranial magnetic stimulation (TMS). As stated previously, there are already several devices approved in the EU, for various indications (including MDD, ASD, Alzheimer's, multiple sclerosis, schizophrenia, smoking cessation, obsessive-compulsive disorder, stroke, chronic pain, migraine, and Parkinson's), that exert their therapeutic effect through transcranial magnetic stimulation.

Although there is no official harmonized document regulating the clinical/therapeutic use of TMS in the EU, there are several articles with recommendation criteria for research and clinical practice with TMS [41,106–108]. The latest was published in February 2020 [41] and recommends TMS with a level A effectiveness (definite effectiveness) for depression, neuropathic pain, and stroke. Updating these guidelines is important for standardizing the types and parameters of interventions with TMS devices in both clinical and research settings.

Before placing these devices on the market, manufacturers need to affix the CE marking on the devices. CE marking can only be affixed after a successful conformity assessment. Usually, these devices are classified as Class IIa.

For moderate and high-risk devices, a Notified Body (NB) must be appointed to carry out the conformity assessment. The manufacturer who intends to affix the CE mark chooses a NB from a list provided by the European Commission.

According to Article 52(6) of the MDR [1], manufacturers of Class IIa devices must perform a conformity assessment to affix CE Mark and place their devices on the EEA market (Figure 6). To do so, they can choose:

- to undergo assessment of the full quality management system (as specified in Annex IX, Chapters I and III), including assessment of the technical documentation (Section 4 of Annex IX) of at least one representative device per device category

or

- to draw up the technical documentation set out in Annexes II and III in conjunction with the conformity assessment as specified in Section 10 (Production Quality Assurance) or Section 18 (Product Verification) of Annex XI. Assessment of the technical documentation shall also be applied for at least one representative device per device category [1].

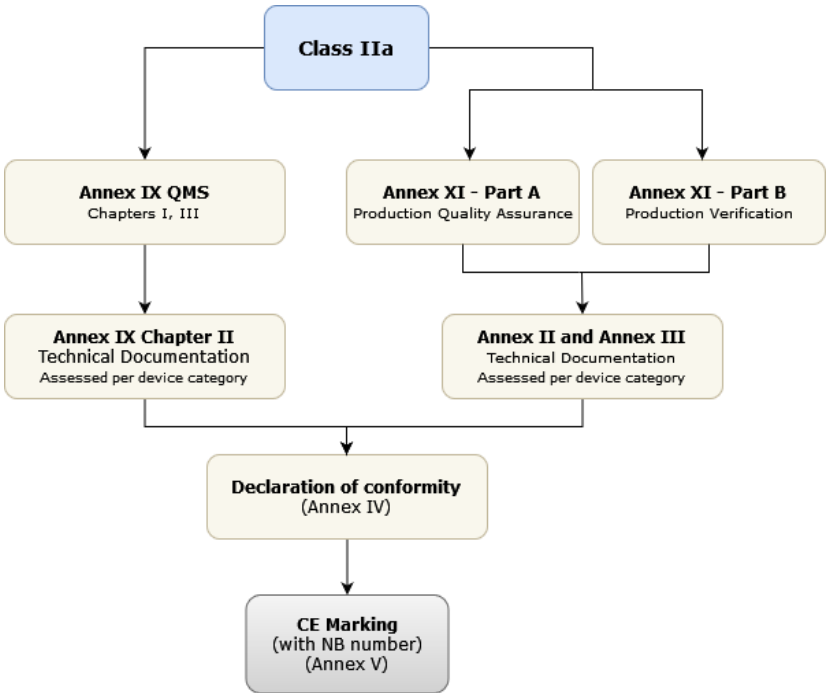

Figure 6 - Flowchart on the options to perform a conformity assessment of Class IIa medical devices.

In Portugal, the SiNATS (National System for Health Technology Assessment), managed by Infarmed, did not conduct any Health Technology Assessment (HTA) and, therefore, there is no reimbursement of this technology by the National Health Service (NHS). Thus, health institutions that want to use this therapy can purchase the devices directly, if they are CE marked. Through a brief online search, it appears that there are at least 5 private clinics in Portugal where TMS is offered for therapeutic purposes.

During the course of this activity, I gained awareness of the unregulated world of DIY Brain Stimulation and the ethical issues that arise from the use of neurotechnologies, which motivated the case study presented before.

The ultimate goal of this activity would be the implementation of a neurostimulation unit, integrated in the NHS. I have searched the literature for the key issues for the implementation and management of a neurostimulation unit. The key issues identified relate to the general context of the unit (medical disciplines, partners involved), the team

composition, environment (proximity to the medical school and hospital), technical equipment, clinical and research activities, target clinical population (eligibility criteria), education and training, ethical aspects (bioethical principles and ICF), and regulatory and reimbursement issues.

I also looked at some health economic studies, which estimated the incremental cost-effectiveness ratio and direct costs of TMS compared with the standard of care. In the case of depression, the QALYs (Quality Adjusted Life Years) gained with TMS are greater than those gained with antidepressants and at lower costs [109,110].

In addition to the ethical issues related to the principles of bioethics in clinical practice and obtaining informed consent, it is also important to highlight the possible ethical issues of not having a neurostimulation unit integrated in the NHS. The issues identified concern depression, which is the disorder where TMS shows greater effectiveness, and include [111]:

- Patients are forced to go to private clinics, which may offer off-label treatments with poorly trained therapists;
- Patients may be encouraged to seek help from internet and start using unapproved tES devices;
- Patients prone to antidepressant side effects and with drug-resistant depression continue to receive sub-optimal treatment, contributing to their individual suffering and to high societal costs;
- In pregnant women, antidepressant exposure has been associated with cognitive impairment in the offspring;
- In the elderly, the effectiveness of antidepressants is reduced, and interaction with other drugs (as they are often polymedicated) constitutes an additional risk.

4.3.5. TMS for Chronic Pain Disorders

Another activity proposed was a review of what has already been done with TMS in chronic pain, for the development of an interventional study with medical device.

This review culminated, in part, in the case study on NIBS research in chronic pain, as it also addresses other neurostimulation methods, namely tDCS, tACS and tRNS.

With this review I learned about the definition of chronic pain, its three main categories (nociceptive, neuropathic and nociplastic), and the biopsychosocial model. This model suggests that pain is a multidimensional, dynamic interaction between biological (such as genetics, age, sex), psychological (depression, anxiety) and social factors (like poor social support, low education level) that influence each other in a reciprocal manner [29].

The prevalence of chronic pain in Portugal and in the world, the standard of care, as well as the overall costs to the NHS were also topics of research. Regarding TMS in chronic pain, I found that the most targeted cortical region is the motor cortex, with evidence suggesting that the stimulation parameters with the best long-term treatment effect are high-

frequency stimulation (≥ 5Hz) of the primary motor cortex (M1), contralateral to the pain side, for chronic neuropathic pain.

The limitations as well as the perspectives/opportunities for clinical studies with TMS in chronic pain were also explored, as demonstrated in the case study. This activity also allowed the study of some brain regions and neuronal networks, as well as the techniques and approaches used in clinical research, in chronic pain and in other neuropsychiatric disorders, namely diffusion tensor imaging (DTI) and voxel-based morphometry (VBM).

4.3.6. H2020 Funding Programme

Horizon 2020 was an EU research and innovation programme with ≈80 billion euros available for the years of the programme's duration (2014-2020). The programme employed different forms of funding, including grants, prizes, procurement and financial instruments. The main types of projects funded by H2020 are Research and Innovation Actions (RIA) and Innovation Actions (IA)[112].

RIAs are collaborative research and development projects aimed at establishing new knowledge or exploring the feasibility of a new technology, product, process, service or solution (including basic and applied research, technology development and integration, testing and validation of a prototype in a laboratory or simulated environment). They are therefore the type of project that can include clinical studies and finance 100% of direct costs and 25% of indirect costs [113].

CRU^{2}C were to participate in a H2020 project as the lead CTU. CRU^{2}C would be responsible for the management of clinical studies, namely preparation of studies' documentation and coordination of ethics and regulatory submissions, monitoring activities, development of eCRFs, and data management and vigilance.

Unfortunately, the project did not obtain funding from the H2020 programme. However, the study of the proposal allowed me to gain a better understanding of aspects related to the preparation, submission, and evaluation of proposals to European funding programmes. In addition, it also allowed me to learn more about the current state of the art in the management of the targeted disease, essentially in terms of screening and treatment.

H2020 proposals were evaluated against excellence, impact, and quality and efficiency of implementation[113]. Excellence concerns the scientific part, and its evaluation considers credibility of the approach, soundness of concept, clarity and pertinence of the objectives, extent of ambition, and innovation potential. The proposal must demonstrate that the project reaches beyond the state-of-the-art. Furthermore, it should emphasize the open science techniques that will be used (includes sharing and management of research outputs), and the engagement of civil society and end-users, when appropriate [113].

Impact includes the expected impacts and the measures to maximize impact and is evaluated considering the dissemination, exploitation of results and communication of activities. The impact section is perhaps the most important section of the application because a novel technology must have a societal, environmental and/or financial impact to demonstrate its value [113].

Quality and efficiency of implementation refers to the work plan (work packages and deliverables), the management structure, milestones and procedures, the consortium, and the resources to be committed to the project. This section is evaluated considering the coherence, effectiveness, complementarity in the consortium, risk assessment, and appropriateness of management structures and procedures [113].

4.4. Deviations from the Activities Plan

Although a monitoring plan and a feasibility assessment had been planned as part of the internship, unfortunately this was not able to occur due to the COVID-19 pandemic context.

5. Discussion

This chapter presents the discussion of the activities that were developed, as well as my point of view on the outcomes and objectives achieved.

Since a great amount of the work developed was focused on clinical studies with medical devices, I was able to gain knowledge in this more specialized area of clinical studies. The theoretical part of the master's degree covering studies of medical devices is nearly entirely made up of an optional curricular unit named "Medical Device Development", which focuses almost exclusively on clinical studies of medical devices as part of the clinical evaluation necessary for placing them on the market.

The traineeship focused not on clinical studies of medical devices that are part of the clinical evaluation for placing MDs on the market, but on investigator-initiated clinical studies, which may or may not qualify as PMCF studies and be part of a PMCF plan. This type of studies has only now been considered in the MDR, as the MDD did not distinguish between the various types of interventional studies of medical devices. The Regulation also now defines the concept of 'sponsor', thus making independent investigators responsible for complying with the requirements of the MDR and facilitating the incorporation of investigator-initiated studies by the manufacturer for regulatory purposes.

This period of internship also allowed to deepen my knowledge of conformity assessment procedures, essentially of Class IIa devices. Ethical issues were also addressed, as these are an important part in the development and evaluation of study protocols.

By contacting both with clinical trials and studies with intervention of medical devices, it was possible to understand the challenges of developing clinical research with medical devices. Medical device studies tend to be smaller in size, more difficult to do participant and practitioner blinding and to have a good control group, as it is difficult to create a sham device that mimics the active one. Also, while drug development follows a process of phase I, II, III and IV trials to test safety, efficacy and toxicity, medical devices have feasibility, pilot, and pivotal study models.

Due to the COVID-19 pandemic, the curricular internship suffered some interruptions, due to the closure of ICNAS, and there were also fewer activities to develop during this time. The biggest difficulty encountered was related to the lack of face-to-face time from which I think I would have benefited greatly. However, the online meetings and e-mail exchanges, and the availability of my internship' tutors, made up for this difficulty.

Nonetheless, the main goals established for this curricular internship were achieved, since I was able to acquire knowledge on the processes and procedures of clinical research, on the new regulations of clinical trials, medical devices, and in some ISO standards, considered essential for the conduction of clinical studies.

6. Conclusion

The internship at an academic clinical trial unit allowed me to gain theoretical and practical knowledge in two of the principal therapeutic areas the CTU covers: neuroscience/neuropsychiatry and oncology. The activities I was able to carry out during the internship were always pre-study activities and part of investigator-initiated clinical studies.

The curricular internship was very enriching, not only at the level of knowledge of procedures that make up the various types of clinical research but also at the level of innovation since all studies/projects mentioned always seek answers to medical challenges.

It served as a complement to the knowledge acquired during the teaching component of the master's degree and added information and training on topics less covered, such as protocol development, specific aspects related to clinical studies of medical devices, clinical trials with radiopharmaceuticals, and addressed regulatory and ethical issues that are hot topics.

The people I had the opportunity to work with were largely responsible for the success of this training experience. At ICNAS, I was very well received by both my internship supervisor and my internship tutor.

The writing of this report enabled me to consolidate the knowledge I gained from this multidisciplinary experience and contributed to my personal and professional enrichment and growth.

In sum, the training experience at CRU^{2}C/ICNAS provided me with a great opportunity to learn about the work that goes on in an academic CTU, to understand its environment and to gain experience in the field of clinical research.

7. References

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