RISK MANAGEMENT IN CLINICAL TRIALS AT CLINICAL RESEARCH SITES

Ana Margarida de Sá Vale

A Dissertation submitted in partial fulfilment of the requirements for the Degree of Masters in Clinical Research Management

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

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"Intellectuals solve problems; geniuses prevent them."

Albert Einstein

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Abstract

Background: With the clinical trials becoming more complex and resource-demanding, it is necessary to improve performance, that is, to achieve the desired result with fewer resources. Effective risk management by each involved party is crucial to the success of a clinical trial. However, there is a lack of guidance and tools specifically developed or adapted to the use of clinical research sites. Such a tool will allow sites to take ownership of their responsibilities and drive their performance within the clinical trials, implementing measures to mitigate the risks.

Aims: The main objectives of this research project are to 1) assess the current risk management methodologies used by Portuguese clinical research sites and 2) develop a tool that seeks to help clinical trials teams to prioritise their actions based on the most critical processes.

Methodology: A survey, created to assess the risk management practices, was conducted among 46 Portuguese sites identified through RNEC and PtCRIN . Moreover, a risk management tool was developed based on Transcelerate's RACT and adapted to the operations under clinical research sites' scope.

Results and Discussion: The surveys' answers show that, although 57% of sites affirmed to have a risk management tool, only nine sites (19.6%) have a structured tool or document to capture the analysis of risks systematically at the site level. A simple, dynamic and flexible risk management tool targeted to sites was developed. It is expected to facilitate risk identification and prioritisation according to its probability and impact. A detailed list of possible mitigations strategies was included in this tool.

Conclusions: The developed tool's implementation may significantly impact the clinical trials' performance by supporting decision-making and promoting efficiency. This work intends to be a starting point to change the clinical trials' mindset by encouraging a more proactive role in managing the clinical trials operations at the site level and fostering the competitiveness of the Portuguese sites in attracting investment for clinical research.

Keywords: clinical trials, risk management, clinical research sites, planning, quality

Resumo

Introdução: Com o aumento da complexidade e exigência dos estudos clínicos com intervenção, torna-se urgente melhorar o seu desempenho, alcançando o melhor resultado com menos recursos. A gestão de risco é crucial para o sucesso de um estudo e deve ser garantida por todas as partes envolvidas. Porém, é notória a falta de diretrizes e ferramentas desenvolvidas ou adaptadas especificamente para os centros de investigação clínica que permitam melhorar o seu desempenho através da implementação de medidas de mitigação.

Objetivos: Os principais objetivos deste projeto de investigação são 1) avaliar as atuais metodologias de gestão de risco utilizadas pelos centros de investigação clínica portugueses e 2) desenvolver uma ferramenta que auxilie a priorização das ações nos centros com base nos processos mais críticos.

Metodologia: Foi realizado um inquérito a 46 centros de investigação clínica portugueses identificados através do RNEC e da PtCRIN. Além disso, tendo por base o RACT da Transcelerate, foi desenvolvida uma ferramenta de gestão de risco, adaptada para a utilização pelos centros de investigação clínica.

Resultados e Discussão: Os resultados do inquérito mostram que, embora 57% dos centros afirmem usar uma ferramenta de gestão de risco, apenas nove (19,6%) têm um instrumento que permite captar a análise de risco de forma sistemática. A ferramenta desenvolvida é simples, dinâmica e direcionada para as operações realizadas pelos centros de investigação. Espera-se que facilite a identificação de riscos bem como a sua priorização com base no seu impacto e probabilidade. Uma lista de possíveis ações de mitigação foi incluída.

Conclusões: A implementação da ferramenta desenvolvida pode ter um impacto significativo no desempenho dos centros de investigação, apoiando a tomada de decisões e promovendo a eficiência. Este trabalho pretende ser um ponto de partida para mudar o paradigma dos estudos clínicos, incentivando um papel mais proativo na gestão das operações pelos centros de investigação e fomentando a competitividade de Portugal na captação de investimento.

Palavras-chave: ensaios clínicos, gestão de risco, centros de investigação clínica, planeamento, qualidade

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List of Abbreviations

ACRO – Association of Clinical Research Organizations

CAC – Clinical Academic Centers

CAPA – Corrective Actions and Preventive Actions

CQMS – Clinical Quality Management System

CRC – Clinical Research Coordinator

CRF – Case Report Form

CRO – Contract Research Organisation

CRU – Clinical Research Units

CTTI – Clinical Trials Transformation Initiative

DPO – Data Protection Officer

EDC – Electronic Data Capture

EEA – European Economic Area

EHRS – Electronic Health Record System

EMA – European Medicines Agency

ePRO – Electronic Patient-Reported Outcomes

EU – European Union

EudraCT – European Union Drug Regulating Authorities Clinical Trials

FDA – Food and Drug Administration

GCP – Good Clinical Practice

GDPR – General Data Protection Regulation

ICF – Informed Consent Form

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC – Independent Ethics Committee

IICT – Investigator-Initiated Clinical Trials

INFARMED – National Competent Authority on Medicines and Health Products (Autoridade Nacional do Medicamento e Produtos de Saúde)

IOM – Institute of Medicine

IRB – Institutional Review Boards

ISF – Investigator Site File

ISO – International Organization for Standardization

KPI – Key Performance Indicator

NHS – National Health System

PI – Principal Investigator

PtCRIN – Portuguese Clinical Research Infrastructure Network

R&D – Research & Development

RACT – Risk Assessment Categorization Tool

RBM – Risk-Based Monitoring

RBQM – Risk-Based Quality Management

RNEC – National Registry for Clinical Studies (Registo Nacional de Estudos Clínicos)

SIV – site Initiation Visit

SOP – Standard Operating Procedure

USA – United States of America

USF – Familiar Health Units

WHO – World Health Organization

1. Introduction

This section provides an overview of the clinical trials within the product development process and introduces the potential benefits and challenges in conducting clinical trials.

Clinical Research Framework

Although bringing up new medicines and technologies into clinical practice is a long, complex, and expensive process[1–3], it is critical to improve patients' healthcare and quality of life. This process has a relatively well-defined timeline from the initial discovery to the product's final launch into the market and its surveillance [Figure 1]. Depending on the health product in development, some steps may have to be added or omitted. Each phase of development is highly regulated by local and international bodies. This research project will focus on the clinical development phase.

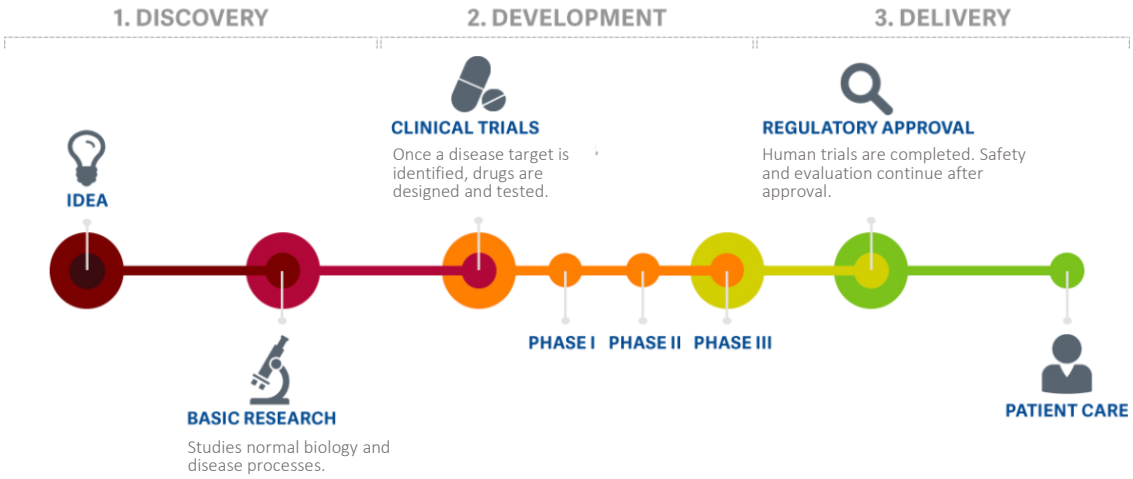


Figure 1 – Product development overview. Source: The GBS/CIDP Foundation International[76].

The clinical development phase comprises the conduct of clinical studies in human volunteers. Clinical studies classification is slightly different across different institutions. In this project, the World Health Organization (WHO) definitions will be used. WHO groups clinical studies in interventional and non-interventional. Interventional studies, also called clinical trials, are defined as “any

research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". Interventions include but are not limited to "drugs, cells, and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care". Non-interventional studies are studies in which the care provided to the participants is not established by a protocol but follows regular clinical practice. This project will focus on clinical trials only.

Clinical trials are generally classified as industry or investigator-initiated trials, depending on the nature of the sponsorship. Additionally, trials using medicinal products are classified in consecutive phases I, II, III or IV according to the trial's objectives and characteristics. The low success rates at each phase dictate a long time and many costs to launch a new product. For example, the probability of launching a new medicinal product from the beginning of phase I, II and III is around 7%, 15% and 62%, respectively[4].

Regardless of the nature of the sponsorship or the phase of the trial, all clinical trials involving medicinal products or medical devices in the European Economic Area (EEA) must be carried out in strict compliance with guidelines on Good Clinical Practice (GCP), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials involving human subjects. These guidelines were published by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that brought together the regulatory authorities and pharmaceutical industry of Europe, the United States and Japan[1]. Adhering to the ICH-GCP guidelines means that trial subjects' rights are respected and clinical trial data are reliable. Today, ICH-GCP guidelines are the standard to conduct trials within the three founding regions and many other countries across the globe[1].

To further harmonise the regulatory requirements of clinical trials with medicinal products, the European Union (EU) published the European Regulation No. 536/2014. Although the Regulation entered into force on 16 June 2014, its application's timing depends on the launch of a fully functional EU clinical trials portal and database[5]. There is a high expectation that this Regulation can simplify the conduction of clinical trials in the EU, namely the investigator-initiated clinical

trials (IICT), due to the introduction of the concept of the low-intervention clinical trials with less stringent rules.

For other types of interventions, legal guidance to conduct clinical trials is limited. However, in 2017, two additional European regulations have been published on medical devices – Regulation No. 2017/745[6] – and on in vitro diagnostic medical devices – Regulation No. 2017/746[7] – that will fully enter into force in May 2021 and May 2022, respectively[8]. Although these regulations are not specific to regulate clinical research, both include an entire chapter dedicated to it.

Potential Benefits and Challenges of Clinical Research

The clinical development phase presents noticeable benefits for the scientific community and patients, specifically for patients who take part in an industry clinical trial where there is a potential clinical benefit of the innovative therapy being studied for the disease's natural history. Moreover, patients might also benefit from early and free access to cutting edge technologies and treatments and enhanced medical care through more frequent and personalised contacts with the medical staff than in routine care[3,9]. The healthcare systems are also relieved as the sponsor takes overall costs with the investigational products, the study-specific diagnostics and treatments, and compensate for the medical and administrative work[3].

On the other hand, clinical trials also impact the economy of a country. According to the European Commission, in 2018, the pharmaceutical and biotechnology industry was the sector with the highest investment in Research & Development (R&D) globally and the second in Europe[10]. Another study from the European Federation of Pharmaceutical Industries and Associations (EFPIA) shows that the pharmaceutical R&D expenditure has been increasing across Europe, the United States and Japan since 1990 [Figure 2], with more than 50% being related to the clinical trials' development phase[11]. When comparing the pharmaceutical industry R&D carried out in each European country, Portugal appears in the 20th position, only above Cyprus, Czech Republic, Greece and Croatia[11].

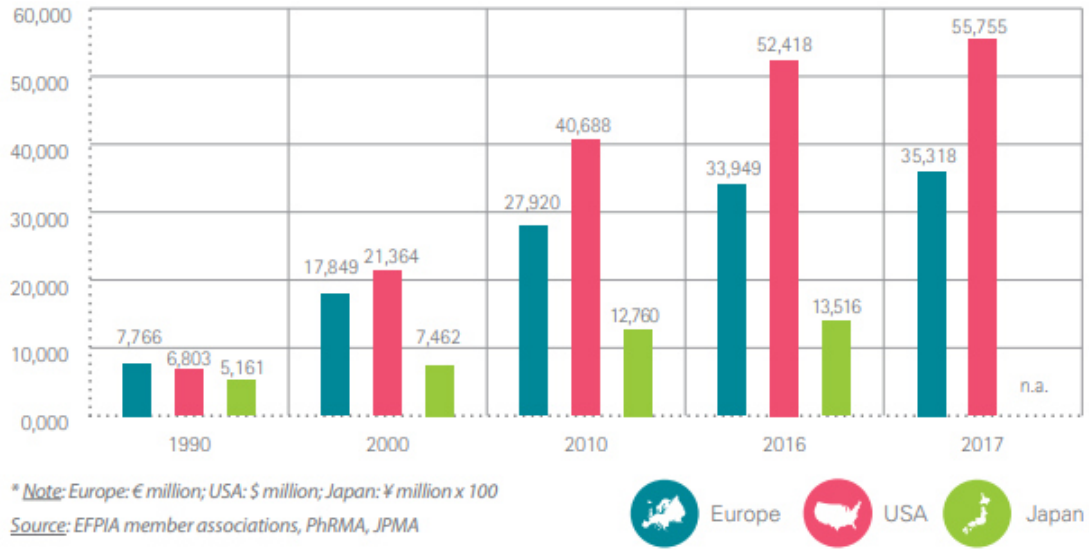


Figure 2 – Pharmaceutical R&D Expenditure in Europe, USA and Japan (million national currency units), 1990-2017. Source: EFPIA*[11].

Furthermore, a PricewaterhouseCoopers (PwC) study requested by Apifarma – The Portuguese Pharmaceutical Industry Association – estimated that, in 2017, the economic impact of clinical trials activity in the Portuguese economy was around 87 million euros, with every euro invested in this sector generating 1.99 euros in the whole Portuguese economy[9]. These data highlight the economic benefit that this sector can bring to Portugal if the ability to compete for both industry and academic investment increases[9].

To better understand the current Portuguese status in terms of clinical trials' activity, the most recent report of INFARMED on the clinical trials statistics published on 12 October 2020 was consulted. According to this document, with data collected from the last semester of 2005 onwards, the annual average of clinical trials approved to be conducted in Portugal is approximately 124. The highest number of clinical trials approved was registered in 2006, with 147 clinical trials approved by INFARMED. Since that date, the number of clinical trials authorised decreased to 87 in 2011 and started increasing from that year onwards. However, the maximum historic number reached in 2006 has not yet been exceeded [Figure 3].

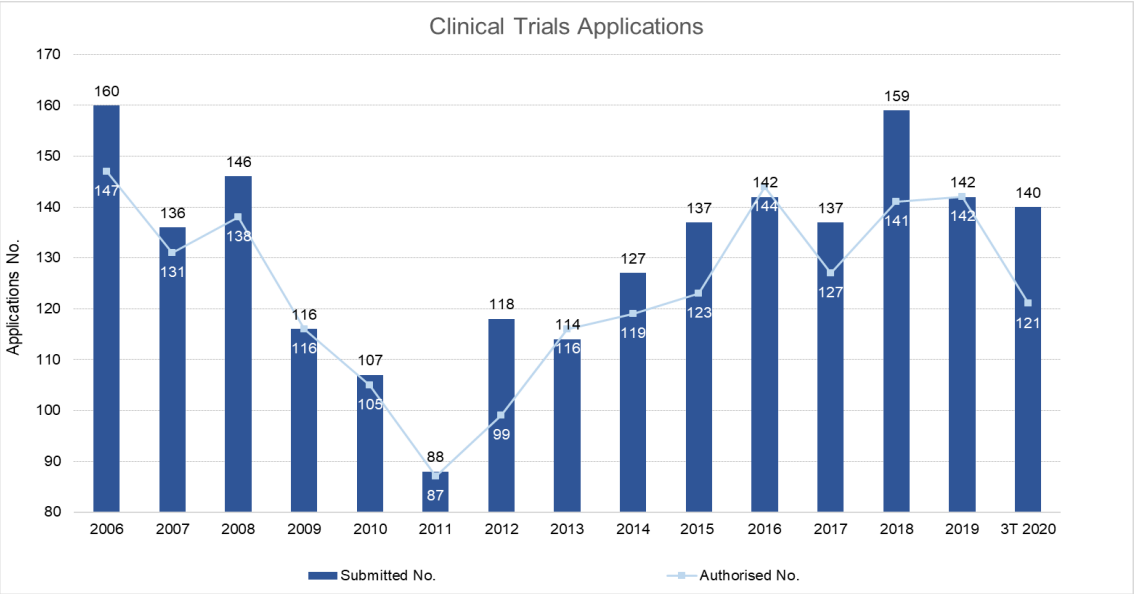


Figure 3 – Number of clinical trials submitted and approved by the Portuguese Regulatory Agency, INFARMED, from 2006 to 2020. Source: INFARMED.

The number of clinical trials performed in each European country in 2019 was collected from the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database to allow comparative analysis. These data refer only to clinical trials with medicinal products. It was observed that Portugal is below the EU average concerning the absolute number of clinical trials performed [Figure 4].

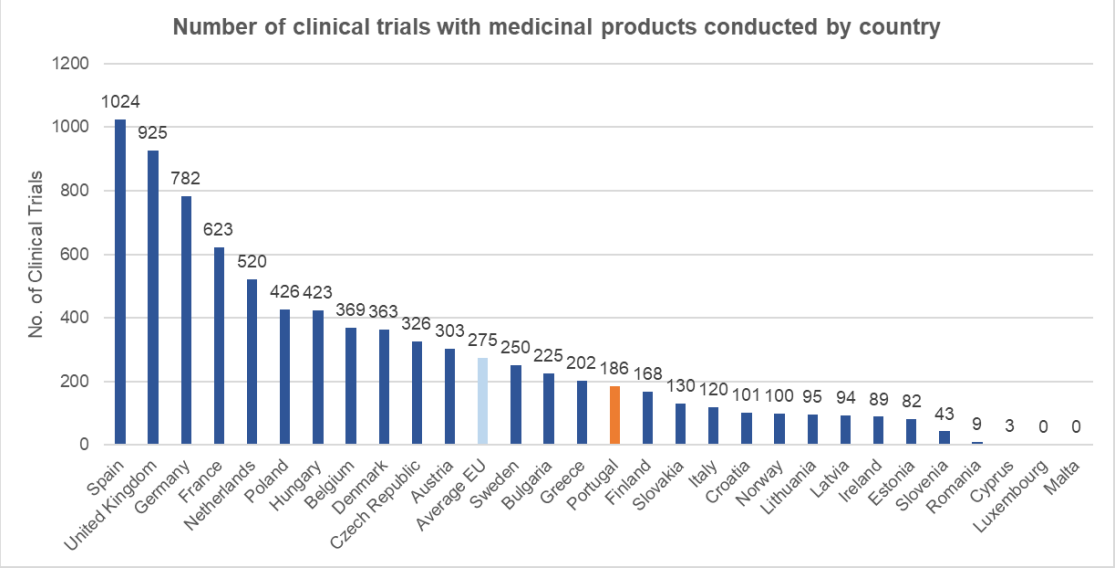


Figure 4 – Number of clinical trials with medicines registered in the EudraCT database by country in 2019. Source: EudraCT database.

The same scenario can be observed by analysing the total number of clinical trials per million inhabitants [Figure 5]. These data show that Portugal has a remarkable margin of progression to significatively increase the number of trials conducted.

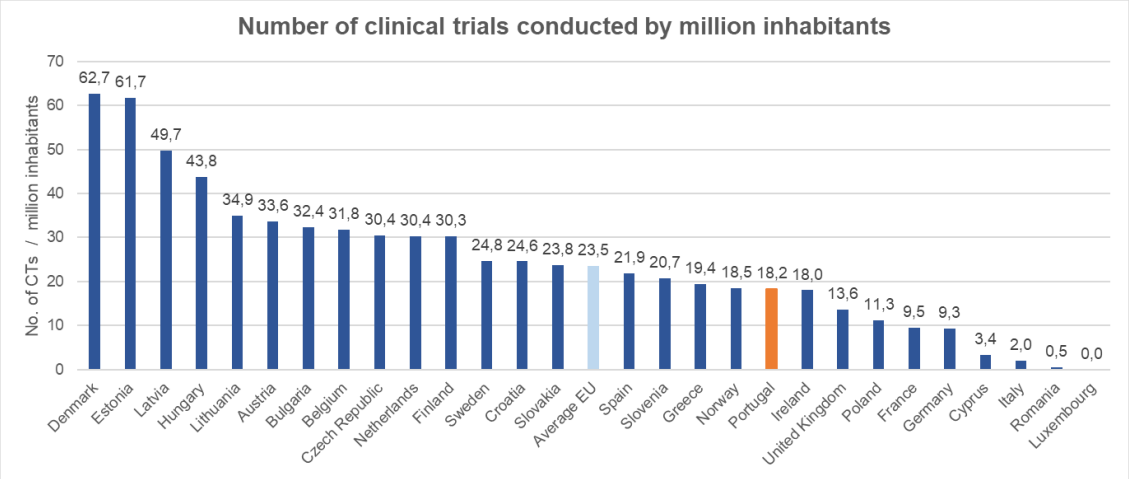


Figure 5 – Number of clinical trials with medicines registered in the EudraCT database by country per million inhabitants in 2019. Sources: EudraCT database; Inhabitants data referred to 2020 according to Statista.Com.

To strengthen the clinical research market in Portugal, it is essential to reflect on its current status, pointing out improvement areas. In 2013, Apifarma released its first report to emphasise clinical trials' economic worth, identifying barriers to their development and bringing up measures to overcome them[9]. In the last report update, dated from February 2019, some of the barriers identified were the lack of valuation of clinical research by the institution's Board of Directors, the inefficiencies of the structures for support research, the insufficient level of professionalisation of research teams or the high complexity of the processes involved in the clinical trials. This study could have been the starting point to equip Portugal with better assets to compete with other countries. However, comparing the reports from 2013 and 2019, it is clear that most of the barriers identified are still the same six years later.

A recent analysis of the Portuguese clinical research sites' strengths highlighted some key factors that can foster the country's attractiveness and competitiveness in this field. The creation of Clinical Research Units (CRUs), also named Clinical

Research Centers (CRC)[12], the quality of healthcare professionals and the good relationship between doctor-patient were pointed out. Based on this reflection, the authors also suggested some actions to enhance the potential identified competitive factors' to improve trial implementation success[13].

Nevertheless, the challenges of clinical trials are not exclusive to Portugal. Thanks to advances in science and technology, clinical trials are becoming more exigent and resource demanding[11]. Therefore, the need for novel adaptative trial designs, the use of software to support trial-related activities, the power of big data, and the strategies to improve quality standards and efficiency are on the involved parties' agendas today[1,2,11].

2. Background

With the clinical trials becoming more complex and demanding, it is necessary to improve performance, that is, to achieve the desired result with fewer resources. This efficiency can be worked through different methodologies whose ultimate objective is to optimise processes and support reasoned decisions to achieve the organisation's goals.

This research project will explore risk management methodology. Thus, this section will include an overview of the risk management process and its application to the clinical research field. Additionally, a summary of potential risks and the evolution of risk culture at different clinical trial levels will be addressed.

Risk Definition

Risk definitions vary slightly across several institutions. The International Organization for Standardization (ISO) 31000 focuses on the risk at the organisation level and defines risk as the "effect of incertitude on objectives". For example, according to the ICH guideline Q9 on Quality Risk Management, the risk is defined as "the combination of the probability of occurrence of harm and the severity of that harm". Although definitions vary, they agree on the essential that is that risk can become an issue if not managed properly.

Risks may apply at different levels. In clinical research, several can be considered as the followings:

- **Program-level**: includes risks that are common to several trials using a given investigational product;
- **Protocol-level**: includes risks that affect a specific project and its design;
- **Country-level**: includes risks that will impact all the sites at a given participating country;
- **Site-level**: includes those risks inherent to the site-specific processes and activities.

The complexity of clinical research requires systematic approaches to actively manage known and emerging risks to accomplish the objectives, saving money

and optimising resources utilisation. A key strategy to do so is through a well-defined risk management process and quality assurance that can guide strategic decisions at every organisational level.

Risk Management Process

The steps defined for the risk management process present slight differences across organisations. However, in general, it comprises the set of activities performed to identify, analyse and control the risks. In this case, the risk management process will be explained based on ISO 31000 [Figure 6]. ISO 31000 applies to all organisations, regardless of its type, size or field, and covers all kinds of risk[14].

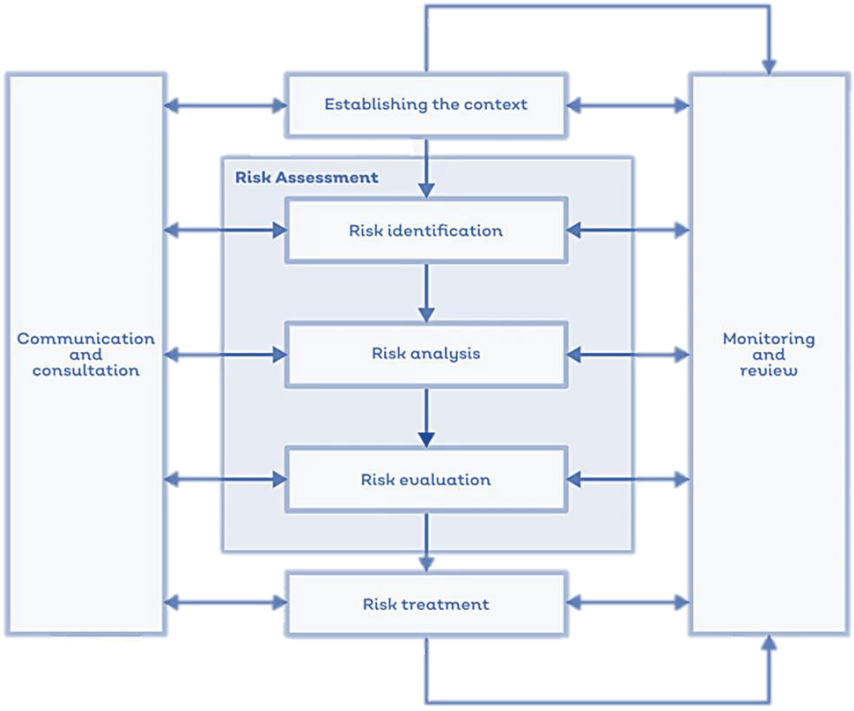


Figure 6 – Risk Management process overview. Source: ISO 31000[14].

Firstly, it is crucial to clearly define and characterise the organisation, sector or activity to which the risk strategy will apply. The external and internal contexts need to be explored and understood, and the scope and objectives that risk management activities are seeking to achieve set. At this phase, the procedures by which the risk management strategy will be implemented should be described and the accountable person or group of people for each activity defined[14,15]. To

ensure all stakeholders' adherence to the defined process, they should be involved in this process from the very beginning[16]. In clinical research, this step includes identifying those processes and data critical to ensure participants' protection and reliability of trial results[1].

Afterwards, the assessment of risks is performed by its identification, analysis and evaluation. Risk assessment is used to map and rate each risk's significance, detail control mechanisms based on its explored causes, and prioritise actions according to the objectives[15,16].

The purpose of risk identification is to reflect on what could prevent the organisation from achieving its objectives[14]. This process can be performed using different techniques such as brainstorming, literature review or competitors' analysis. During this phase, the information gathered is crucial to support the identification and description of the highest number of risks possible[14]. Risk categories and sub-categories may also be used to facilitate risk identification process[16]. In clinical research, risks categories may vary depending on the stakeholder (sponsor, Contract Research Organisation (CRO), site, among others) or the scope of the analysis (study design, preparation, conduct, analysis, among others)[16].

After the risks are identified, an effort should be made to comprehend the risks' sources and causes, prioritise risks and determine controls[14]. There are several quantitative and qualitative methodologies to analyse the priority of risks based on the probability of occurrence and the severity of harms[17,18]:

1. **Probability**: addressing how likely the given risk is to occur, that is, the likelihood that the risk will materialise and become an issue.
2. **Severity/Impact**: addressing the extent of what would happen if the risk occurred, that is, the potential impact that the risk, if it materialises, will have on the goal not being achieved.

Some risk management methodologies also consider a third dimension in the risk analysis:

3. **Detectability**: the ability to detect the harm, that is, the extent to which the issue would be detectable[19].

Each dimension is classified based on simple relative scales, being the most common the 3, 4 or 5 points scales[20]. The total risk score is then given by the product of the two (or three) dimensions scores and can be captured through a matrix similar to the one represented in Figure 7 used by the National Health System (NHS) of the United Kingdom.

			Likelihood				
			1	2	3	4	5
			Rare	Unlikely	Possible	Likely	Almost certain
Consequence	5	Catastrophic	Moderate Risk (5)	High Risk (10)	Extreme Risk (15)	Extreme Risk (20)	Extreme Risk (25)
	4	Major	Moderate Risk (4)	High Risk (8)	High Risk (12)	Extreme Risk (16)	Extreme Risk (20)
	3	Moderate	Low Risk (3)	Moderate Risk (6)	High Risk (9)	High Risk (12)	Extreme Risk (15)
	2	Minor	Low Risk (2)	Moderate Risk (4)	Moderate Risk (6)	High Risk (8)	High Risk (10)
	1	Negligible	Low Risk (1)	Low Risk (2)	Low Risk (3)	Moderate Risk (4)	Moderate Risk (5)

Figure 7 – Risk Analysis Matrix used by NHS. Colours represent the risk score: green coloured boxes mean low risk; yellow boxes moderate risk; orange boxes high risk; and red boxes extreme risk. Source: Elmontsri (2014)[75].

The risk evaluation consists of comparing the resulting scores with the established risk criteria and decide on its priority and the most suitable response strategy[14,21]:

- **Acceptance**: risks can be accepted by dealing with their consequences if they ever happened;
- **Avoidance or elimination**: risks can be avoided or eliminated before their onset by changing the approach to the task leading to the risk;
- **Transfer**: risks can be transferred, for example, to an external supplier or insurer;
- **Treatment**: risks can be solved by implementing control and mitigation strategies.

During the risk treatment phase, controls are specified along with the plans to implement them. When selecting the mitigation strategy, the organisation's objectives, the risk thresholds and the available resources must be considered.

Some controls defined may also introduce new risks that need to be managed, which points out that risk management is a continuous process[14].

Consequently, all stages of this process need to be reviewed and monitored to assess if actions implemented effectively reduce risk and, if applicable, define additional actions based on new knowledge and experience. It is also essential to update risk assessment according to context or objectives' changes and track actions' implementation[14,16]. Risk review might include reconsidering original risk decisions to accept, avoid, eliminate, transfer or treat the risk. If there are no treatment options available or treatment options do not sufficiently reduce the risk, the risk should be recorded and kept for periodic review[14].

All risk management activities should be documented to support future decisions on risk management[16] and facilitate communication within the organisation and between the relevant stakeholders. Responsibilities for monitoring, reviewing, communicating and reporting should be clearly defined in the risk management plan[16].

Following this overview of the risk management process, the current status of its applicability to the clinical research field will be explored.

i. Risk to healthcare organisations

In this sub-section, it will be considered that healthcare organisations may include hospitals, primary care institutions, clinics, pharmacies or home care services. It should also be noted that once clinical trials are conducted at healthcare organisations, the risks impacting their structural organisation, facilities, equipment or staff will consequently affect the conduction of clinical trials activities. When referring to the healthcare institutions as the location where trial-related activities are conducted, the terms "clinical research site" or just "site" are used.

Following the insurance crisis of the 1970s, the Institute of Medicine (IOM) issued a disruptive report entitled "To Err is Human: Building a safer health system". This report drew the public's attention to the need of reducing the medical errors and their consequences and improving patients' safety through the design of a safer health system[22]. To illustrate this point of view, the authors' emphasised that the

medical error is not a consequence of healthcare professionals' incompetence or bad intentions, rather a result of the healthcare system implemented[22,23]. The report suggests that healthcare organisations should ensure well-designed processes to prevent, recognise, and mitigate patients' harm from error, highlighting that preventive actions have the most significant potential effect[22,23].

This document received extensive media coverage and triggered the immediate action from the healthcare industry, non-governmental organisations and federal government. It is also associated with an increased number of research grants and publications on patients' safety in the intervening years[24].

Two years after this first report, the IOM released a new report, in 2001, named "Crossing the Quality Chasm: A New Health System for the 21st Century". This second report focused more broadly on how the healthcare system can be re-designed to innovate the patients' experience and improve care quality, thus reducing the "chasm"[25].

According to this report, a good healthcare system is defined by the following six complementary vital dimensions:

- **Safety**: avoiding patients to be injured by the care that is intended to help them by creating a safe environment that works for all patients at any time;
- **Effectiveness**: using clinical expertise and scientific knowledge to provide the care that produces better outcomes comparing with the available alternatives, including the alternative of doing nothing;
- **Patient-centeredness**: providing care that is respectful and responsive to individual patients' preferences, expressed needs, and values and ensuring that patients are informed and involved in all medical decisions;
- **Timeliness**: reducing waiting time and delays for patients to receive care, preventing them from experiencing emotional distress or physical harm;
- **Efficiency**: obtaining the best value possible from the available resources, avoiding waste;
- **Equity**: providing care that does not differ in quality because of personal characteristics such as, but not limited to, gender, ethnicity, age, geographic location, disability or socioeconomic status.

These principles can also drive clinical research because, when conducted in patients, it constitutes an option to provide health care. Subjects that participate in clinical research will also be impacted by the existing risks for patients followed by regular clinical practice. We will look more deeply for a set of common risks among healthcare organisations and its extrapolation for the clinical research field.

Data Privacy and Protection

The digital revolution in the last few years is having a marked impact on the development of several industries, and the health sector is not an exception. However, this revolution also brings along foreseeable concerns regarding data privacy and protection. In response to this challenge, the regulators have been increasing the demand for measures that might prevent or mitigate the risk of data breaches.

The EU, for example, has implemented new and harmonised requirements on how organisations should collect, store and process the personal data of individuals living in the EU or the EEA. This regulation – General Data Protection Regulation (GDPR) no. 2016/679 from 27 April 2016 – is effective from 25 May 2018, and all organisations handling data from European citizens must comply with the document, regardless of their geographic location[26].

This regulation brings some innovations to the legislative framework as the reinforcement of citizens' rights regarding their data management. The requirements are even stricter for special categories of personal data that, according to this document, includes "data concerning health"[26] and therefore affects both regular care and clinical research.

In line with this regulation, healthcare organisations were required to define a Data Protection Officer (DPO) who is the contact person for any question related to the patients' data processing. The DPO's contacts must be provided to the subjects participating in clinical trials through the Informed Consent Form (ICF). Moreover, suppose data processing is likely to result in a high risk to individuals' rights and freedoms, as in clinical research. In that case, the sponsor must carry out a Data Protection Impact Assessment (DPIA) to determine risks for data

handling and compliance with the regulation. Although not accountable for this analysis, healthcare institutions are responsible for ensuring that their policies, processes, and systems comply with the requirements for data processing[27].

The GDPR implementation leads the healthcare organisations to start defining processes and preventive measures to ensure compliance and avoid penalties and reputational consequences. However, not all organisations were well-prepared. In a study conducted among Portuguese health clinics almost six months after the enforcement of the GDPR, only 12% of the 57 clinics surveyed confirmed they had fully implemented the GDPR[28].

Currently, the clinical practice is becoming completely dependent on the Electronic Health Records Systems (EHRS), broadly used to record and keep health data, prescribe medication, or request medical exams. With the development of digital solutions, cybercrime comes as a real issue. This is especially concerning in the healthcare industry due to the nature of data maintained and protective measures' weakness that reflects the underinvestment in information technology infrastructure[29].

In the last few years, several ransomware attacks involving health units around the world have been reported[30]. These attacks are characterised by the encryption of data, blocking access, followed by the demand of payment to unlock it[29,30].

The cybersecurity has been raising the attention of Portuguese entities and regulators, which, in January 2017, established the mandatory notification of safety incidents that occurred in the public healthcare institutions to the Ministry of Health[31]. Later in September, a new Portuguese law has been published to guide the implementation of cybersecurity politics in healthcare[32].

In clinical research, data are collected from the subjects' medical records. With almost all healthcare institutions using EHRS, cyber-attacks on these systems can also impact the clinical trials, constituting a relevant risk for this activity. According to the 2nd revision (R2) of ICH-GCP, sponsors should ensure and document sites' computerised systems' validation. This process includes verifying the consistent fulfilment of requirements for completeness, accuracy, reliability and intended performance throughout the trial. This guidance also adds

that “the approach to this validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results”. From the sites’ perspective, ICH-GCP (R2) recommends the maintenance of Standard Operating Procedures (SOPs) to describe system setup, installation, and use, including system security measures and processes of change control, data backup and recovery, contingency planning, and decommissioning.

Certainly, security incidents will continue to happen. However, healthcare organisations need to invest in personnel and technology that allows the development of robust processes and preventive measures to control and lessen the risk of data breaches and cyberattacks on the patients’ data. Failure to do so can lead to the patients’ harm either in regular clinical practice or in clinical research.

Workforce Engagement

Healthcare professionals drive healthcare organisations, and therefore risks affecting these professionals will impact the overall institution performance. Similarly, the clinical research field is also affected as the clinical trials teams are constituted by healthcare professionals employed by such organisations.

A study conducted in the United States of America (USA) in 2014 showed a considerable difference in burnout prevalence among physicians (48.8%) compared with a control group of working USA adults (28.4%)[33]. Through the conduction of a similar survey completed by more than 15.000 physicians worldwide from June to September 2019, the 2020 Medscape National Physician Burnout & Suicide Report indicates that 42% of the physicians reported they are burned out[34]. The prevalence among Portuguese physicians is in line with the global results (43.6%); similar results were found among nurses (49.4%)[35].

The burnout definition varies due to the subjectivity of its diagnostic criteria. However, it is often defined as a syndrome caused by chronic exposure to job-related stress, resulting in emotional exhaustion, a feeling of demotivation and depersonalisation, and lack of a sense of effectiveness and personal accomplishment[33,36]. Burnout of healthcare professionals has a significant impact

on the quality of care provided and personnel turnover, which in turn imply the quality of the healthcare system and patients' satisfaction. On the other hand, it can also decrease their willingness to participate in clinical research activities as these extra activities will increase the burden already existing.

Risky situations should be identified early and preventive measures implemented to avoid future harm. Healthcare organisations are an essential contributor to their professionals' wellbeing by promoting autonomy, providing adequate material resources and supporting staff, providing flexible scheduling and creating a fair balance between effort and reward[36]. The current tendency of high effort and low reward can be counteracted by implementing performance-related payment schemes for healthcare professionals.

In Portugal, salary is the predominant method of remuneration of health professionals. However, in 2006 a reform to the primary care setting has introduced, besides salary, the payment of incentives based on performance within the Familiar Health Units (USF). Some factors considered on the assignment of such incentives are related to productivity, accessibility and quality objectives[37]. This model has already shown a positive effect in the disease control among patients followed at the USF compared with other primary care units[38]. Clinical research involvement could also be considered an important dimension to assign financial incentives to health professionals.

Clinical trial staff at the sites is seriously impacted by their experience within their clinical practice. Some of the most common barriers pointed by clinical staff to not participate in clinical research is the lack of time, training, resources and support by leadership[39,40]. Consequently, improved working conditions are more likely to increase their engagement with clinical research-related activities. On the other hand, engagement with research can positively impact these employees' performance within its clinical practice by encouraging new skills' development, professional growth, and career progression.

Emergency Preparedness

The healthcare organisation's operations can be significantly affected or even made unavailable due to a natural disaster or harmful actions. When disaster

strikes in an industry as complex as healthcare, the effects can be far-reaching and harm patients' lives. Therefore, healthcare organisations are recommended to have plans to ensure patients and staff safety during a disaster and ensure its ability to continue operations when, simultaneously, the organisation works to recover from a disaster[41]. This issue gained an enormous relevance due to the COVID-19 pandemic started in 2020 that test the healthcare organisations' preparedness for emergencies.

The COVID-19 pandemic rapidly led to a large and atypical influx of patients that increase the pressure on the NHS, challenging the clinical support to COVID-19 and non-COVID-19 patients. In Portugal, a study compared the data regarding hospital scheduled and urgent activity from March to September in 2019 with the corresponding period in 2020[42]. This investigation revealed a decrease of 14% in regular medical appointments corresponding to one million fewer consultations conducted in 2020. The impact was higher to patients without a diagnosis and, therefore, without an established therapeutic scheme. This conclusion is based on the reduction of first medical appointments (-23%) that has been higher than for subsequent appointments for patient follow-up (-11%). The global urgency observations suffered a reduction of 35% compared to 2019, corresponding to 1.3 million fewer observations, which seems to indicate the population's fearfulness to seek healthcare services. The number of surgeries was 30% inferior in 2020. Regarding the healthcare workers, the same study also reported an additional 32% of absences from work in 2020 across all professional groups.

The additional burden on the health services and staff has an obvious impact on clinical trials. Many investigators were reallocated to work in emergency medical care and support other teams, limiting their availability to the clinical trials' activities. Participants may also miss the visits due to the risk of infection or the self-isolation requirements, which can difficult the clinical oversight by investigators[43]. These challenges could impact clinical trials' conduct, namely the completion of protocol assessments, the provision of the investigational products, or the recruitment activity[44].

It is estimated that 80% of non-COVID-19 trials were stopped or interrupted[45]. Data extracted from ClinicalTrials.gov between January and July 2020 show that the number of non-COVID trials decreased from January 2020 to May 2020,

showing an increment of trials activity starting in June 2020 [Figure 8a][44]. According to the same analysis, June was also the month where the number of the study suspensions released was higher than the number of new suspensions [Figure 8b], pointing out the recovery point.

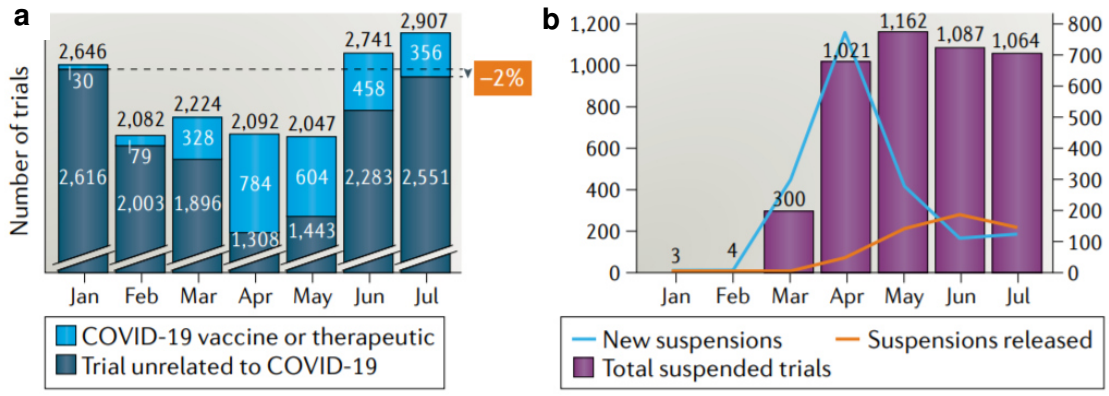


Figure 8 – Global clinical trial activity variation from January to July 2020 in terms of the number of trials (a) and the number of trials' suspensions (b). Source: Xue, John Z et al. (2020)[44].

This challenging phase taught that certain aspects and processes of clinical trials' design, conduct, and reporting have a significant margin for quality improvement, benefiting participants, investigators, and research-related stakeholders[45]. In many trials, sponsors and sites join forces, searching for alternative processes to address inefficiencies and limitations imposed by COVID-19. Some of these alternatives seem to endure, such as the incorporation of technology in everyday trial activities.

Many other risks to healthcare organisations could also be described and extrapolated to the clinical research field in this section as they are intrinsically related. It is important to retain that the risk-based decisions at the organisations level will directly or indirectly impact clinical trials performance. Ultimately participants' safety should be ensured.

Risk management in clinical research

As demonstrated in the previous section, healthcare is a risky business, and the clinical research field is not an exception. As it is well-know, the success rates of clinical trials are very low, and the causes underlying these failures are several:

- **Demonstration of efficacy or safety**: A study observed that among 640 phase III trials, 30% fail due to inadequate efficacy and 9% because of safety concerns[46].
- **Budgeting and financing**: In the same previous study, it was showed that 12% of trials failed due to lack of funding[46].
- **Eligibility criteria**: Among more than 3400 clinical trials across different development phase and therapeutic areas, more than 40% had amended protocols before the first subject enrolment, being 16% of the amendments related to the eligibility criteria, resulting in delays of trial timelines by 4 months[47].
- **Subjects' recruitment**: Studies conducted at the beginning of the 21st century reported that around 80% of clinical trials do not accomplish the enrolment target on time phase[48].

A risk culture among clinical research stakeholders can contribute to diminishing the probability of occurrence of such failures.

For several years, in the clinical trials field, risk has been associated only with the risk for participants' safety and rights. However, risks affecting other stakeholders should also be considered: for the study participants, the sites and study teams in charge of the study conduct, the sponsors, the vendors providing supporting services, the governance structures or the public health bodies. Stakeholders have different and complementary responsibilities in the project's quality assurance and must consider its level of risk concerning their responsibilities and duties to the project's quality assurance[16].

i. Risk from the perspective of participating subjects

There are some benefits for patients to participate in clinical trials such as the early access to innovative therapies for their medical condition, more frequent contacts with the medical team, medical care for free or the chance to contribute to future developments regarding their medical condition[49].

However, clinical trials also involve potential risks for the participant subjects. Risks vary from trial to trial depending on, but not limited to, the trial design, target population or study procedures required. When a subject accepts to participate in a clinical trial, they are willing to accept its potential benefits and risks.

Regarding the risks, they are mainly associated with which treatment the participants will receive during the clinical trial. If they receive an experimental treatment, they have the risk of experience potential unknown or unexpected side effects that could be more serious than the ones known for the standard treatment. Furthermore, the experimental treatment may show no efficacy on the subjects' conditions or lower efficacy than the standard treatment. Participants can also be assigned to the control arm, which means the subject receives the standard treatment or placebo and may not experience the potential clinical benefits from the experimental treatment[49].

Besides the risks related to the treatment itself, there are also risks associated with study procedures that can cause additional burden or inconvenience on the participant. For example, medical appointments could take more time than usual, and subjects may need to travel to the research site more often or even stay at the site for a longer period. There is also an increased risk of data breaches as participants' data are shared outside the institution. In this case, additional measures, such as data anonymisation, have to be implemented[26].

The sponsors may also need to put in place additional protective measures when the trial allows the inclusion of vulnerable populations such as children, elderly population, pregnant or breastfeeding women or individuals with mental illness. For example, for vulnerable groups that cannot give full consent, sponsors must ensure that an alternative consent process is available, such as obtaining consent by a legally responsible proxy[50].

At the beginning of the 21st century, when there were no regulations regarding the ethical use of human subjects in research, some atrocious and harmful research projects raised public awareness and debate. These research studies led to the development of regulations and guidance to avoid and reduce the risks to participants in clinical trials[51].

The first international document issued with this objective was the Nuremberg Code, in 1947, in consequence of the judgement of German physicians who conducted abusive medical experiments with prisoners during the 2nd World War without their consent, causing severe harms or even death to the participants. This document established ten ethics principles that should govern medical research with humans, including voluntary participation after providing consent and the maxim that the benefits must outweigh the risks[50,51].

However, research projects not compliant with these defined principles continue to occur along the second half of the 21st century, as raised by Henry Beecher, in 1966. This doctor published an article demonstrating that unethical research was still being conducted even in democratic countries and reputable research institutions[51]. In response to these continued disrespect for the Nuremberg Code, other publications were released, such as the Declaration of Helsinki, in 1964, issued by the World Medical Association, or the Belmont Report, in 1979, written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research established in the US[50,51].

The ethical principles and reflections recognised in these documents support the creation of the reference document for nowadays' clinical research design and conduct around the world, the ICH-GCP. The compliance with the requirements defined in the ICH-GCP regarding clinical research ensures that risks for trial data and participants are avoided or reduced and that their rights, safety and well-being are respected[1].

Among the protective measures implemented worldwide to protect trial participants is the mandatory ethical review of the trial protocol by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Other requirements include the need for well-defined processes to obtain an informed consent or monitor the safety of the investigational product.

Every research institution needs to establish an IRB or IEC to conduct an ethical review of the trial protocol before the trial's initiation and before every substantial amendment required during the trial. These entities are responsible to provide an ethical opinion on, among other things, the trial protocol and its procedures, the suitability of the investigators and facilities to conduct the trial, and the methods and materials to be used in obtaining the informed consent of the participants[1]. Without an ethics favourable opinion, the clinical trial cannot be initiated or the ongoing amendments implemented.

As already discussed, informed consent must be freely obtained in writing for every trial participant after he/she is informed about all aspects of the trial and voluntarily confirm his/her willingness to participate. During the trial, when an amendment impacts the participants' safety, they need to be informed about the new safety information and re-consent to continue in the trial, by signing another Informed Consent Form (ICF) or an ICF amendment.

This safety information is continuously assessed by reviewing adverse events reported during trials or, in case treatment is already marketed, through the pharmacovigilance processes. During the trial, the regulatory authorities continuously evaluate the risk-benefit ratio of an experimental treatment and monitor safety signs that can put the trial continuity at risk and lead to the trial authorisation revoke. With this objective, sponsors need to report, within 7 to 15 calendar days, any serious or unexpected adverse event to the regulatory authorities. All other safety events and concerns are regularly submitted to the authorities in periodic reports entitled Development Safety Updated Report, (DSUR)[1].

In some trials, the sponsor also established an Independent Data Monitoring Committee to assess, at a regular basis, the progress of the clinical trial regarding its critical efficacy and safety endpoints and to recommend to the sponsor whether to continue, modify, or stop a trial[1].

In summary, risks to the trial participants are still present. However, nowadays, there are many well-established measures to minimise and control these risks and ensure that participants are protected.

ii. Risk from the perspective of regulatory authorities

In the first decade of the 21st century, the ICH consortium recognised the importance of a quality system in the pharmaceutical industry by publishing two important guidelines: ICH Guideline Q9 on quality risk management (2006) and ICH Guideline Q10 on pharmaceutical quality system (2008). Although these documents apply to the pharmaceutical industry as a whole and not directly impact the clinical trials' activity, they have raised awareness for the development of such guidelines to the clinical research field[19].

Over the last years, clinical trial management has been changed from a conservative approach, with the objective of ensuring zero defects, to a risk-based approach by which areas of greatest risk are identified and prioritised. This mindset change is a consequence of the increased complexity and globalisation of clinical trials and technological evolution. In response to this evident changing environment on studies conduction, several guidance and consultation documents have been issued by the health regulatory authorities. These documents highlighted the need to improve clinical trial processes' efficiency by encouraging the use of risk-based quality management systems to identify, prioritise and control risks systematically.

In 2011, the Food and Drug Administration (FDA) published a guidance document focused on monitoring activities only[52]. This paper determined a change in the FDA's preferred model for sponsors to meet their monitoring activities from a 100% verification of all data onsite to a risk-based monitoring approach. FDA supports this decision on several publications that show that certain data anomalies may be more readily detected by centralised monitoring techniques, now possible due to the advances in the use of electronic data recording. It is also argued that these techniques can help sponsors to improve oversight on the most critical aspects to subject protection and data quality.

In 2013, the European Medicines Agency (EMA) also published a reflection paper intended to facilitate the implementation of a risk-based approach to quality management of clinical trials. According to this document, the risk management process should start as early as possible to allow the mitigation strategies to be incorporated in the protocol and other trial-related documents, such as the monitoring plan.

Following these guidance documents, and as a consequence of the evolution in clinical trial processes, the ICH-GCP, first published in 1996, was revised in 2016[1]. The objective of this amendment was "to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results". In this new version of ICH-GCP, the implementation of a quality management system based on a risk approach was introduced as a sponsor's responsibility throughout all stages of the clinical trial development process. In this document, the consecutive phases recommended to be incorporated in this system are described: critical processes and data identification, risk identification, evaluation, control, communication, review and reporting. Regarding reporting responsibilities, it is mentioned that the sponsor should record the deviations from the predefined quality tolerance limits and the preventive and corrective actions taken in the clinical study report. It is also suggested that the sponsor develop risk-based strategies for data monitoring[1].

The increasing risk culture also impacted the lawmakers. Based on the recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials of 10 December 2012[53], the European Clinical Trials Regulation no. 536/2014[5] introduced the categorisation of clinical trials according to their risk. The definition of a low-intervention clinical trial was set as a trial where "the intervention poses only very limited additional risk to the subject compared to normal clinical practice". This concept includes trials with marketed products used under their marketing authorisation or which use is supported by published evidence, guidance or established medical practice. As a consequence of presenting lower risks, those clinical trials are "subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products"[5]. It is expected that this new legal framework simplifies the conduction of clinical trials with lower risks, such as most investigator-initiated trials, promoting the growth of clinical research activity in the EU.

These documents and guidance show a growing predisposition among regulators and consultation institutions to recognise risk management as a best practice to prevent risks and optimise clinical trials' performance and resources utilisation.

The regulatory authorities are also implementing these practices in their inspection activities. Due to the high number of products requesting a marketing authorisation and participating sites by trial, it is not feasible to inspect all of them. Consequently, risk-based approaches for selecting the potentially problematic clinical research sites to be inspected have been implemented. For example, FDA signed an agreement with an external vendor, CluePoints, to develop and test a software to support site inspection processes by comparing sites data patterns and identifying the outliers[55].

iii. Risk from the perspective of sponsors

In the last years, sponsors and CROs have taken steps to implement risk management approaches as a strategy to improve data quality and make clinical trials more cost-efficient. The risk-based monitoring (RBM) methodology is a striking example.

Following the FDA guidance published in 2011, sponsors and CROs started to develop tools to implement RBM in their clinical trials. However, no well-understood and tested methodologies were available at the time, and the development of such strategies to successfully deploy and scale RBM was a huge challenge.

TransCelerate BioPharma Inc., from now only referred to as TransCelerate, was launched in 2012 as a non-profit organisation that joins more than 20 biopharmaceutical companies to design and facilitate the implementation of solutions developed to drive the efficient, effective and high-quality delivery of new medicines. One of the first projects developed by TransCelerate was the RBM initiative, earlier in 2012, that sought to develop a model approach for RBM based on the regulators' guidance. The developed standard model for RBM can be adapted by any organisation, regardless of the clinical trial type or phase. Moreover, lessons learnt from the implementation of the RBM model, piloting to trials sponsored by their member companies, were shared.

This model has the centralised and off-site monitoring activities as the foundation of monitoring efforts, complemented by on-site monitoring activities targeted according to a Monitoring Plan based on the trial risk assessment. This plan should allow the increase or decrease of monitoring activities according to the continuous risk analysis throughout the trial. The model includes five phases, as described below:

1. **Risk Assessment**: Identification, analysis and evaluation of the clinical trial's risks. To facilitate and systematise this process, TransCelerate developed and made available The Risk Assessment and Categorization Tool (RACT). It aims to support sponsors in the establishment of the baseline monitoring requirements based on the overall risk level (high, medium or low) of a given trial. This tool will be further explored in the next sub-section entitled "Risk Assessment and Categorization Tool (RACT)".
2. **Critical Data & Processes**: Definition of the trials' data or processes that support decisions about the investigational product's efficacy and safety profile. The level of monitoring may be higher on those critical data and processes.
3. **Quality & Risk Plan**: Specification of potential risk indicators and corresponding thresholds which, once reached, should trigger an action, such as increased or decreased data monitoring or site follow-up. In 2014, TransCelerate created a risk indicator library with more than 140 risks than can be chosen and adjusted by sponsors depending on the trial.
4. **Monitoring Plan**: Description of trial-specific monitoring approach, including remote and onsite activities. TransCelerate has adopted two different concepts to distinguish the review of source data for quality and protocol compliance – referred to as Source Data Review (SDR) – from the comparison of the Case Report Form (CRF) data against the source to check transcription accuracy – referred to as Source Data Verification (SDV).
5. **Monitoring Execution**: Implement the monitoring plan and assess the impact of the RBM approach by measuring changes in quality, time of data collection and issue resolution, and operations efficiency.

Simultaneously, large-size biopharmaceutical companies and CROs started to develop their own RBM models[56]. However, the practical implementation is still low among sponsors due to: the fear of compromise the whole clinical trial data by a failure in the planning or execution of the RBM model; the lack of internal knowledge and procedures; the creation of new roles and the adaptation and training of the existing ones according to new responsibilities and required skills; or the management of sites and participants' expectations[57,58]. This adaptation is even demanding for small to medium size companies and academic trials. Beyond the reasons previously pointed out, in the academic setting, the lack of knowledge and training on risk management and the increased costs of information technology to support centralised monitoring, such as Electronic Data Capture (EDC) systems, cause an additional burden[59].

After the second revision of ICH-GCP, the implementation of RBM strategies become a legal requirement, and the number of RBM studies increased exponentially. According to a survey conducted among the members of the Association of Clinical Research Organizations (ACRO), in 2016, only 18% (n=1797) of the studies started utilising RBM methodology while, in 2018, this percentage increased, reaching 61% (n = 1944) [Figure 9].

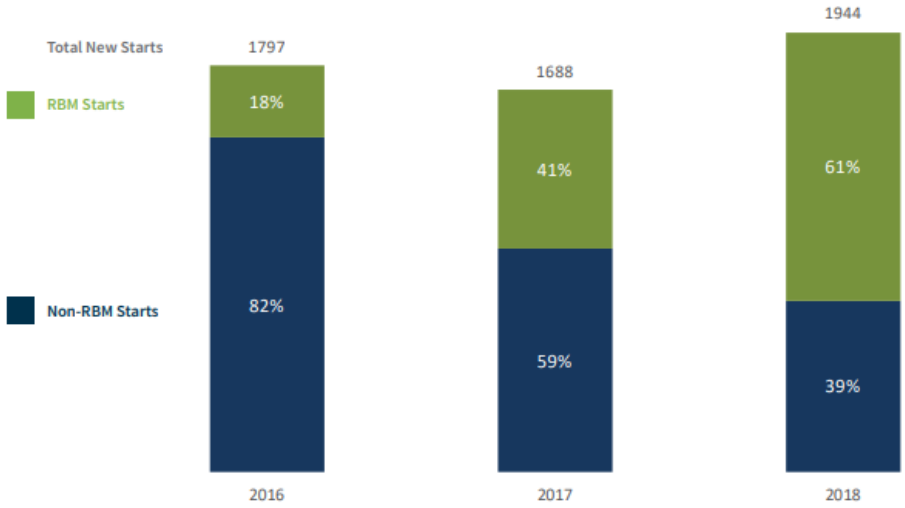


Figure 9 – Percentage of starting trials using RBM approach by year among ACRO members surveyed in 2016, 2017 and 2018. Source: ACRO[77].

The second revision of ICH-GCP also highlighted the need for the extent of the risk-based methodology to cover the whole trial execution instead of monitoring activities only. Furthermore, the ongoing revision of ICH E8 (R1), on general considerations for clinical studies, includes a new section regarding clinical studies quality. The draft version emphasises that the monitoring, auditing or inspection are "an important part of a quality assurance process but are not sufficient to ensure the quality of a clinical study".

Consequently, the industry is now re-thinking the application of the RBM underlying principles to the development of an integrated quality system that can be applied to the design, planning, conduct and analysis of the trial. From the several entities that have recently published recommendations on the implementation of such quality approaches, the majority have their route on "Quality by Design" principles, defined in 2011 by the Clinical Trials Transformation Initiative (CTTI), a public-private partnership founded by the FDA and Duke University[60]. In the clinical research field, these systems are commonly designated by Clinical Quality Management System (CQMS) or Risk-Based Quality Management (RBQM).

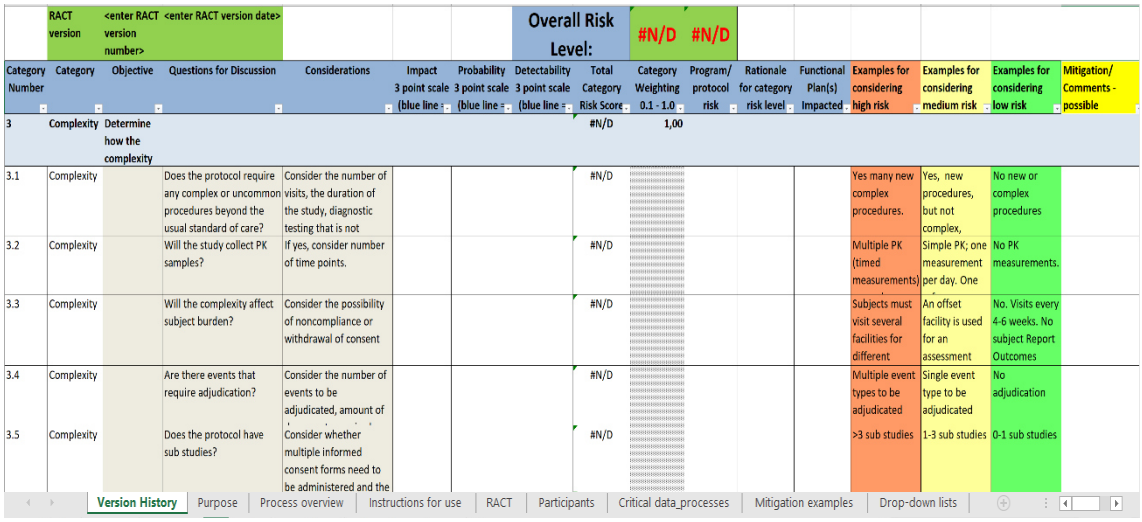
The RBM methodology and RBQM/CQMS should be aligned on the fundamental risk principles to avoid confusion within the organisation or among stakeholders. However, due to these shared principles, both concepts can be misleading. Therefore, it is essential to note that RBM constitutes a risk control methodology that is part of the RBQM/CQMS[61].

Risk Assessment and Categorization Tool (RACT)

This tool intends to support sponsors in risk assessment and treatment at the protocol level by identifying questions and considerations for discussion and possible risk mitigation strategies for implementation. The final objective is to determine the overall risk score of a trial and define the baseline level of monitoring activities according to the TransCelerate's risk-based monitoring position paper. The mitigation strategies defined should be incorporated in the trial-related document, such as the monitoring or the statistical plan.

TransCelerate highlights that this is a non-validated tool and do not intend to be a pre-defined checklist to be completed. Instead, its content should be adapted according to the sponsor's or trial's needs.

The RACT is an Excel-based tool with several spreadsheets [Figure 10]. The sheet with the tool itself presents some questions to guide a cross-functional discussion through the risk management process. These questions are organised by categories such as Safety, Study Phase, Subject Population or Investigational Product/Study Medication.



	RACT version	<enter RACT version number>	<enter RACT version date>					Overall Risk Level:	#N/D	#N/D						
Category Number	Category	Objective	Questions for Discussion	Considerations	Impact 3 point scale (blue line =	Probability 3 point scale (blue line =	Detectability 3 point scale (blue line =	Total Category Risk Score	Category Weighting 0.1 - 1.0	Program/ protocol risk	Rationale for category risk level	Functional Plan(s) Impacted	Examples for considering high risk	Examples for considering medium risk	Examples for considering low risk	Mitigation/ Comments - possible
3	Complexity	Determine how the complexity						#N/D	1,00							
3.1	Complexity		Does the protocol require any complex or uncommon procedures beyond the usual standard of care?	Consider the number of visits, the duration of the study, diagnostic testing that is not				#N/D					Yes many new complex procedures.	Yes, new procedures, but not complex,	No new or complex procedures	
3.2	Complexity		Will the study collect PK samples?	If yes, consider number of time points.				#N/D					Multiple PK (timed measurements)	Simple PK; one measurement per day. One	No PK measurements.	
3.3	Complexity		Will the complexity affect subject burden?	Consider the possibility of noncompliance or withdrawal of consent				#N/D					Subjects must visit several facilities for different	An offset facility is used for an assessment	No. Visits every 4-6 weeks. No subject Report Outcomes	
3.4	Complexity		Are there events that require adjudication?	Consider the number of events to be adjudicated, amount of				#N/D					Multiple event types to be adjudicated	Single event type to be adjudicated	No adjudication	
3.5	Complexity		Does the protocol have sub studies?	Consider whether multiple informed consent forms need to be administered and the				#N/D					>3 sub studies	1-3 sub studies	0-1 sub studies	

Version History | Purpose | Process overview | Instructions for use | RACT | Participants | Critical data_processes | Mitigation examples | Drop-down lists

Figure 10 – Risk Assessment and Categorization Tool (RACT) template. Source: TransCelerate.

Using a 3-point scale of low (1 point), medium (2 points) and high (3 points), the following total scores can be calculated through the RACT:

- **Individual risk score:** after manually scoring the probability, impact and detectability of a given risk, its total risk score is automatically calculated by the product of these scores.
- **Category risk score:** after manually scoring the probability, impact and detectability of a given category, its total risk score is automatically calculated by the product of these scores. RACT also allows the assignment of a weighting factor to each category;
- **Trial risk score:** Based on each category's risk score and weighting factor, the overall trial risk score is automatically calculated.

The tool also provides three columns with examples that can be considered during the risk analysis to support the scoring process. In Table 1, three examples extracted from the RACT are presented.

Table 1 – Examples of considerations including in RACT to support the risk scoring process. Source: TransCelerate.

Category	Questions for Discussion	Examples for considering the high risk	Examples for considering the medium risk	Examples for considering the low risk
Safety	Is the compound a marketed product?	The compound is not a marketed product.	The compound is a marketed product but is being studied in an unapproved indication.	The compound is a marketed product and is being studied in an approved indication.
Complexity	Will the complexity affect subject burden?	Subjects must visit several facilities for different procedures […] or subjects requiring domicile visit […]	An offset facility is used for an assessment during the study, […] or subjects will be domiciled at least twice for 24 hours.	No. Visits every 4-6 weeks. No Patient-Reported Outcomes (PRO) assessments.
Investigational Product/Study Medication	What is the route of administration?	Subject self-administration of injectable.	Oral administration; multiple times/day.	Controlled intravenous administration in the acute care setting […].

The sheet designated as “Mitigation Examples” provides a non-exhaustive list of mitigations, such as considering protocol re-design or adjust monitoring strategy.

RACT is a useful tool for sponsors as a starting point to discussions on risk assessment at the protocol level. However, the tool also presents some limitations, such as risk scoring's subjectivity due to lack of thresholds and strict criteria defined for each risk level. Considering that this tool needs to be completed by different functional groups, the lack of audit trail and the high risk for Excel automatic formulas to be corrupted between changes are relevant limitations. Some companies have designed technological solutions to address these limitations. Such solutions also bring additional features like the integration of risk libraries and the improved visualisation of the results through user-friendly dashboards[62].

iv. Risk from the perspective of the clinical research sites

Despite the different tools and approaches to manage clinical trials' risks at the sponsor or protocol level, these seem insufficient as some activities are intrinsically dependent on the sites' performance.

A study conducted, in 2012, by the Tufts Center for the Study of Drug Development (Tufts CSDD) showed that, among 151 global clinical trials, 11% of sites fail to enrol a single subject and 37% fail to achieve the targeted enrolment expectation[63]. Another study conducted, in 2016, by the same institution revealed that, on average, nearly 11% of sites selected are never activated, and the start-up phase is still very long – around 5 to 6 months total duration[63].

These delays represent additional costs for sponsors. Therefore, as part of their mitigation plan, sponsors have developed more robust feasibility methodologies to select sites that ensure better performance. The sites' feasibility is the process by which sponsors evaluate the site's capabilities to support successful project completion in terms of its objectives, timelines and costs. Some of the factors considered in the feasibility phase are the clinical experience, the sites' infrastructures, equipment and trial-dedicated resources, the prior experience in clinical trials and the overall quality and performance[64].

A study showed that sponsors tend to select sites they had already collaborated with as they already have knowledge from previous site-sponsor collaborations to support the decisions[48]. During the feasibility process, sponsors can review past audits or inspections reports available for these sites[64], but most commonly, they analyse the Key Performance Indicators (KPIs). The KPIs, such as the enrolment rate, timelines of data entry or protocol deviations rate, are collected by sponsors during a trial[65]. These indicators are then useful during future feasibility processes by allowing to predict the site's performance for a new trial.

However, the main objective of collecting these KPIs is to adapt the monitoring activities at the site risk level[65]. When a high-risk KPI is identified at a site, the sponsor inquires the site to understand the possible causes. Consequently, based on this discussion, the sponsor suggests some corrective and preventive actions to be implemented at the site upon its agreement. In this case, this high-

risk KPI could trigger the sponsor to improve the monitoring efforts to follow-up on implementing the agreed actions.

It is generally noted that, although the risk management process at the site level is a matter of concern, it is not owned by the site and it depends on the sponsor's initiative. However, the sites should take accountability of risk management activities in the operations under their scope. This attitude is expected to enhance their performance and strengthen the cost savings that sponsored trials can bring.

A study conducted in Portugal by PwC, upon Apifarma's request, showed that the clinical trials activity, in 2017, generated savings in public expenditure estimated at 10.8 million euros. These savings correspond to the amount borne by sponsors with investigational products, including the comparators or placebo, and diagnoses and therapeutic examinations that are usually in charge of the Portuguese National Health System (NHS)[9].

These data support the benefit that sites can reach by adopting a more proactive role in the management of their risks and issues. By collaborating with several sponsors, sites have excellent knowledge about common issues and possible mitigation strategies. However, this accumulated experience is not being reflected in the systematisation of processes and implementation of measures to improve their performance.

A well-known way to systematise this knowledge is through the implementation of SOPs. According to the ICH-GCP (R2), the SOPs are "detailed, written instructions to achieve uniformity of the performance of a specific function". Sites can use SOPs to set standards for those responsibilities legally attributed to the investigators and, consequently, subject to inspection. Sites that operate under SOPs and maintain them suitable to address its purpose demonstrate its commitment to clinical research and its ability to ensure consistent processes throughout the trial and across several trials[66].

In Brazil, for example, in 2009, the national regulatory body – ANVISA – published guidance for the preparation of GCP inspections conducted by them[67]. This document identifies a list of critical SOPs that are mandatory for the clinical research centres to maintain and present in case of inspection. Although there is no data regarding the effective improvement of sites' performance, data show a

significative increase in the number of clinical research projects approved by Brazilian ethics committees from 2007 to 2011[68].

The development of specific tools for sites' use could allow sites to take ownership of their clinical research responsibilities and drive their performance. These tools are not intended to replace the sponsor responsibilities on risk management, which are mandatory by regulations, but rather complement them.

The infrastructures that support clinical research, with physical and human resources, within the sites may also play a vital role in implementing a risk management culture. In Portugal, the law no. 61/2008 created the legal framework for Clinical Academic Centers (CAC), defined as integrated infrastructures to provide clinical care, training and research support[69]. There are currently eight CACs in Portugal that bring together healthcare organisations, higher education institutions, and/or research institutes. The newly created Agency for Clinical Research and Biomedical Innovation (AICIB) is responsible for the external evaluation of CACs every four years. The first evaluation process will occur in 2021 and, depending on the performance results achieved, CACs have access to a financing program[70]. This is expected to raise awareness of the importance of performance improvement and risk management.

Although the number of CACs is still low, most hospital health units in Portugal have a Clinical Research Unit (CRU), that is, a dedicated infrastructure that centralises and manages all clinical trials activities at the hospital[70]. This entity is not covered by Portuguese law.

Although the distinction between these two terms was provided, CRU will be used along this dissertation to globally refer to infrastructures that support clinical research at the clinical research sites.

3. Scope and Aims

Clinical trials involve potential risks that can affect human participants' safety and clinical trial data's reliability. Failing to accomplish these objectives will jeopardise the clinical trial's overall validity and, consequently, the resources spent in its conduct. Therefore, it is fundamental to identify the potential risks, analyse them and establish plans to manage them even before the clinical research project starts. This process can significantly impact the clinical trials' performance, supporting decision-making and promoting the more sustainable and efficient use of clinical research resources.

Even though risk management is having considerable attention from the stakeholders in the last years, it is still needed a more in-depth assessment of the risks that may arise in the different phases of clinical trial implementation and the strategies that can be implemented to mitigate them upstream.

Many published papers share the lessons learnt from a given clinical trial, identifying the common challenges noted during its conduct and suggesting some solutions to avoid or prevent reoccurrence in future. However, in these cases, issues are explored separately and based on a single clinical trial or site experience. These challenges are often presented from the sponsors' perspective, discussing what they can do differently in future trials concerning their design and planning.

Clinical research sites play a vital role in the success of a clinical trial. Therefore, it is urgent to understand how their contribution can be improved. This work seeks to provide an integrated approach to risk management in clinical trials' operations at the site level.

The main objectives of this research project are to:

a) assess the implementation level of risk management procedures in clinical trials operations by Portuguese clinical research sites;

b) develop a simple and intuitive tool that allows clinical teams to prioritise their actions based on the most critical processes.

4. Methodology

In order to meet the goals of this research project, a survey was created, and a risk management tool was developed. This section describes the methodology used from the preparation of the survey to the analysis of the data obtained as well as the step-by-step process for the development of the risk management tool.

Survey to clinical research sites development

i. Preparation and validation

A survey was developed to assess clinical research risk management practices among clinical research sites in Portugal [Appendix A].

The specific objectives of the survey were:

1) To know if clinical research sites in Portugal identify and discuss risks of clinical trials at the time of the trial feasibility process;
2) To identify the reasons behind the decision of clinical research sites to perform, or not to perform, a risk assessment;
3) To describe the most common risks identified by the Portuguese clinical research sites;
4) To identify the most valuable features that clinical research sites expect from a risk assessment tool.

The survey was based on the instrument developed by Hurley and colleagues[59] adapted from the original version from the CTTI. It was then adapted based on the national context and the review of the current literature.

Population

The survey was developed to be distributed among the Portuguese healthcare institutions that participate in clinical trials. The list of participants was based on the public registers available at the electronic portal for registry and publication of all clinical studies undergoing in Portugal – RNEC, which stands for National

Registry for Clinical Studies – and in the information provided by PtCRIN, the Portuguese Clinical Research Infrastructure Network.

From 1 January 2017 onwards, all clinical trials with medicines, medical devices and cosmetic products in Portugal shall be submitted exclusively through RNEC. The involved sponsors, clinical research sites, local ethics committees and principal investigators must also be registered. All entities or individuals available at the platform had authorised the public disclosure of recorded data at the registration time.

All entities registered in RNEC under the "Clinical Study Site" category were analysed and duplicates removed. Duplications occurred mainly due to the register of different clinical departments within the same institution. To a lesser extent, duplications were also due to slight differences in the institution's name, for example, with the use of abbreviations or conjunctions. In the case of private hospital groups that aggregates several institutions, the group was contacted instead of the individual institutions that were also excluded. In addition to this exclusion criteria, one institution was not contacted as contact details were not publicly available. Therefore, through the analysis of the RNEC platform, a total of 60 institutions were contacted.

As RNEC only allows to capture sites performing clinical trials with medicines, medical devices or cosmetic products, PtCRIN was also contacted. PtCRIN is a national infrastructure focused on the promotion of national and international cooperations in clinical research for the development of Investigator-Initiated Clinical Trials. By contacting PtCRIN's members and other entities identified by PtCRIN, it was also possible, for example, to include sites that perform clinical trials with nutritional or behavioural interventions. The contact details were collected from public sources, such as the entities' websites, publications, public databases and a master's thesis[72]. Based on the available sources, eight additional clinical research sites were contacted beyond the ones registered in RNEC.

Therefore, the total number of institutions contacted was 68. This number includes hospital centres, local health units, hospitals (public, private, or public-private partnerships), specialised clinics and research institutions.

Only one answer by institution was considered. In case more than one completed survey was received for the same clinical research site, only the last one received was considered.

The survey was, whenever possible, directly sent to the person responsible for the clinical research activity at the site, namely managers or collaborators of the Clinical Research Units (CRU).

Sample size

The sample size was defined as 35 completed surveys. This size was calculated based on the following formula:

$$Sample\ Size = \frac{\frac{z^2 \times s(1-s)}{e^2}}{1 + \frac{z^2 \times s(1-s)}{e^2 N}}$$

N, population size | e, Margin of error | z, z-score | s, standard deviation

The population size, N, was established based on the total number of institutions registered in RNEC after removing duplicates – 60 – and an estimated number of 10 other institutions to be identified by other sources.

Due to the small size of the total population represented and the high level of uncertainty associated with the fact that no previous studies were found, a confidence level of 90%, a margin of error of 10% and a standard deviation of 50% were used.

Ethics and Data Protection

The survey was reviewed and approved by the Ethics Committee of the NOVA Medical School (CEFCM) on 23 April 2020 [Appendix B].

Regarding data protection, as the GDPR applies to personal data about individuals and does not govern data about companies or any other legal entities, this survey is out of its scope.

Institution identification was mandatory to ensure that duplicate answers were identified and excluded from the final analysis. The data collected was aggregated and anonymised for analysis, and therefore it is not possible to assign any data to a specific institution.

In the first question of the survey, the respondent representing the clinical research site had to consent to disclose the data. Otherwise, it was not possible to complete it.

Data obtained from the survey can also be used to support other publications. Future publications will also comply with the data protection measures described above.

The survey results will be kept for two years after the date of publication of this dissertation or until the records are no longer required to support the protocol, whichever date is later.

Validation

The validation phase was to collect feedback regarding the time to completion, questions' construction and readability, and suitability of the content to the defined objectives. During this phase, the survey was reviewed by clinical research professionals from different clinical research sites.

The survey was initially sent to four professionals from different institutions. The feedback received was analysed and led to survey modifications. The main changes implemented were:

1. The addition of a field to briefly describe the risk assessment methodology used by sites, if any; and
2. The restriction up to three options of the reasons indicated to justify the use, or not, of a risk assessment methodology.

The new survey version was sent for another four people from four additional institutions to repeat the feedback process. After this new round of feedback, only minor changes were implemented. Therefore, this version was used as the final one.

None of the answers obtained during the validation process was considered in the final analysis.

ii. Request to answers

The survey was coded to a web application for online survey creation named EUSurvey, developed and maintained by the Directorate-General for Informatics of the European Commission (DIGIT). The survey was accessible through a web link.

The survey was available from 12 May 2020 to 30 June 2020. All survey questions were mandatory, and therefore it was not possible to submit an incomplete survey.

The survey was sent by e-mail to all the pre-identified clinical research sites. Afterwards, weekly reminders were sent by e-mail for the sites with no answer submitted by that date. For non-respondent institutions whose phone contacts were available, reminders by phone were also performed. After a total of five contacts, the institutions were identified as non-respondent and no further reminders were performed.

iii. Data and statistical analysis

The Microsoft Office Excel was used for descriptive analysis of data obtained. Data were represented as sums, percentages and relative and absolute frequencies. Descriptive tables and graphics were also obtained using Microsoft Office Excel.

The IBM Statistical Package of Social Science (SPSS) Statistics version 25 was used for analyse correlations between variables. As the variables under analysis are qualitative and the sample size is small, Fisher's Exact Test was performed. A confidence level of 90% was used.

Risk Management Tool development

i. Risk Identification

The risks that were included in this tool were identified based on the following online available sources:

1. **Risk Assessment Categorization Tool (RACT)** developed by TransCelerate to help sponsors identifying the risks that could affect the subject safety, data quality and regulatory compliance in a clinical trial. The tool also allows the sponsors to calculate the trial risk level based on the identified risks' probability, impact and detectability.
2. **Risk Indicator Library**, a collection of risk indicators created by TransCelerate to allow for more rapid detection of possible issues to investigate or mitigate further.
3. **Summary of EMA GCP inspections**, documented in the Annual Report of the Good Clinical Practice Inspectors' Working Group, published on 12 March 2020. It describes the GCP inspections carried out by the EMA in 2018.
4. **Summary of FDA inspections**, inspectional observations reported by the FDA and its representatives in 2020 (data available from the 1st of January to the 30th of September).
5. **Inputs from the survey**, specifically to the question: "What risk(s) do you identify in your clinical research site that could compromise the compliance with the ICH-GCP and the performance of the clinical investigational teams in a clinical trial?"

The documents mentioned above (1. to 4.) were developed essentially for sponsors' use. Therefore, it was a need to exclude some risks whose control or action are not within the scope of the clinical research sites. For the same reason, some risks have also been adapted to focus on the part of the process under the clinical research site's responsibility.

ii. Risks Categorisation

The risks were grouped into categories to facilitate the search for a specific topic within the tool. The categorisation was based on the categories defined in the Risk Indicator Library and RACT, both created and made available by TransCelerate. Some categories were merged or naming adapted to focus on the clinical trials' activities that the clinical research sites can manage. Also, the categories that include activities that depend exclusively on the sponsor, concerning trial design and logistical operations at the protocol level, for example, were not considered.

The following seven categories were defined to group the risks identified:

- **Safety**: focuses on the safety of the investigational product concerning adverse reactions and unexpected events, its report and management.
- **Complexity**: focuses on the complexity of trial-related procedures, including uncommon procedures beyond the usual standard of care, the existence of sub-studies, multiple vendors and outsourced services, blinding requirements and technological expertise.
- **Subject Population**: focuses on eligible population and subjects' recruitment, retention and withdrawal.
- **Data Collection**: focuses on the data quality, type of data source, CRF completion and adherence to data entry instructions and timelines.
- **Investigational Product**: focuses on the management of the investigational product cycle within the site from the receipt of the supplies to its destruction or return to the sponsor.
- **Essential Documents**: focuses on the site's management and storage of the critical documents to the trial.
- **Staffing, Supplies & Equipment**: focuses on staff turnover, training needs and delegation of responsibilities; and the suitability, maintenance, calibration and storage of trial's supplies and equipment.

iii. Potential Causes & Controls

The defined risks were analysed to determine possible reasons that could lead the risk to become a real issue. These reasons were described in the “Potential Causes” column of the tool.

Each reason described was then investigated further to determine possible actions that may prevent the issue from occurring or that may mitigate its consequences on the site’s performance. Similarly, these actions were described in the column “Potential Controls/Mitigation Actions” of the tool. A column was added to allow the identification of the person or group of people accountable for implementing the defined actions.

Both the causes and the controls for each reason were identified through: 1) the review of scientific reports and publications, and 2) brainstorming based on personal clinical research experience. Regarding the scientific publication's search, the PubMed database was used; only full-text available articles were reviewed. The Google search was also used to capture the grey literature produced about this topic, such as reports, dissertations or working documents. The source documents used were identified in the column “References” of the tool.

iv. Risk Assessment Model

For this tool, a more straightforward 3X3 matrix for risk assessment was incorporated. There is a column to enter the probability assessment and another column to enter the impact assessment. For each variable, the user will choose one of the three available options from a drop-down menu. Based on these two values chosen by the user, the tool will automatically calculate the total risk score, according to the following formula:

$$\text{Risk} = \text{Probability} \times \text{Impact}$$

The final score is given in the column “Total Risk Score” on a 3-point scale of “Low”, “Moderate” and High” risk. By visualising the different total risk scores, clinical research sites can prioritise the implementation of the mitigation actions.

The 3 X 3 matrix was chosen as it is quick and easy to apply. For the risk assessment model's decision, it was considered that clinical research sites have none or limited experience with risk assessment methodology.

v. Design and layout

The layout of the tool was defined based on the following:

1. **Risk Assessment Categorization Tool (RACT)**, an Excel-format tool developed by TransCelerate
2. **Inputs from the survey**, specifically to the question “How important do you consider the following characteristics/features for a risk assessment tool?”

Having RACT as the starting point, some columns were excluded to simplify its use. Only essential columns to the tool’s comprehension and completion were kept and adapted to this tool’s purpose. The final layout was constituted by the following columns: Category, Identified Risk, Probability, Impact, Total Risk Score, Potential Causes, Potential Controls/Mitigation Actions, References and Responsible.

Excel was the platform chosen for the tool creation as this software is widely available at clinical research sites, and its use is practical and straightforward. Excel also offers dynamism to the tool and autonomy to users who can filter, add or remove risks as applicable for a given clinical trial. This means that the tool's content can be adapted in a case-by-case depending on the clinical trial specificities or the clinical sites culture.

5. Results and Discussion

In this section, the results of the survey will be presented and interpreted. Similarly, the final version of the risk management tool will also be shared and discussed in light of its applicability, benefits and limitations.

Risk management practices in Portuguese clinical research sites

The survey results will be used to reflect on the current risk management practices at the Portuguese clinical research sites. The survey can be consulted in Appendix A.

i. Demographics

From the 60 clinical research sites identified via RNEC platform, 43 answers were received (response rate of 71.7%). In the same way, from the eight additional sites identified through PtCRIN, three answers were received (response rate of 37.5%). Overall, from the 68 clinical research sites contacted, 46 were receptive to collaborate in this survey (overall response rate of 67.6%). A list of the respondent institutions is provided in Appendix C.

Figure 11 shows the roles performed by respondents within the clinical research site. The majority of surveys were completed by Clinical Research Coordinators (46%) – who are professionals directly involved in the execution of clinical trials processes at the site – or by Clinical Research Unit's (CRU) Managers (33%) – who are accountable for defining and controlling those processes' execution. These results showed that the survey has been answered by the defined target population.

These data also allowed to observe that most respondent sites have professionals fully dedicated to clinical research activities, and at least one third have a CRU for the coordination and management of clinical research activities. These results did not reveal if these professionals support all the clinical trials performed at the site or only a specific department or therapeutic area.

In some smaller sites, clinical trials go through the Clinical Director's approval and are often coordinated directly by the investigators and clinical staff involved.

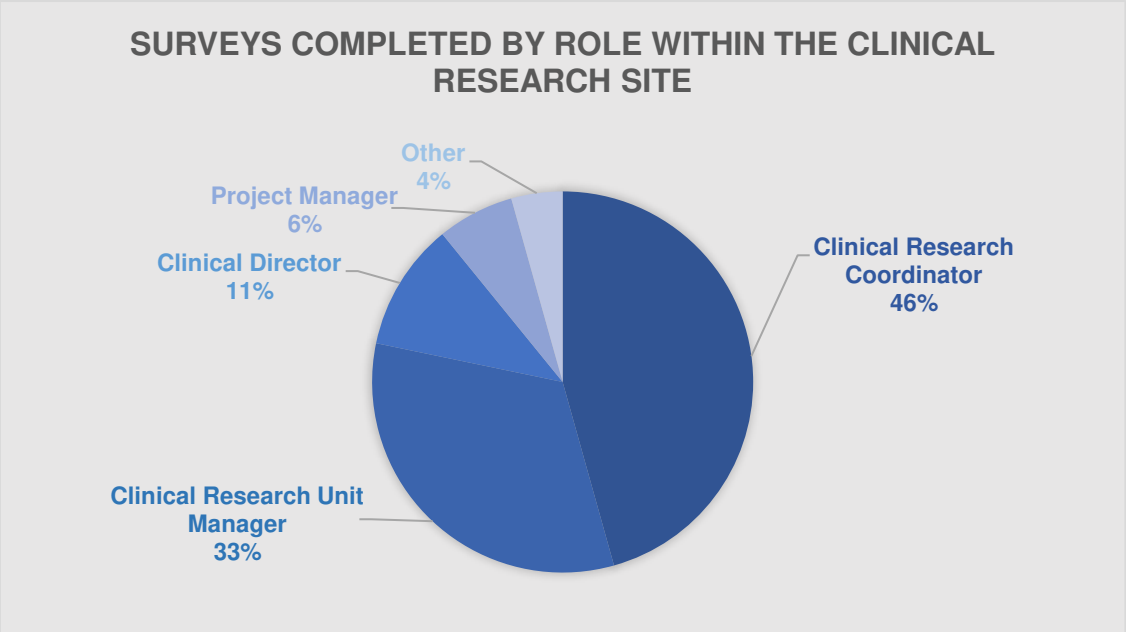


Figure 11 – Results of the survey's question "Please indicate your role within the clinical research *site/institution."*

Regarding the number of clinical trials conducted in the last two years, among the sites that collaborate in this research, one third started less than five trials, one third started from six to thirty trials, and one third started more than thirty trials [Figure 12].

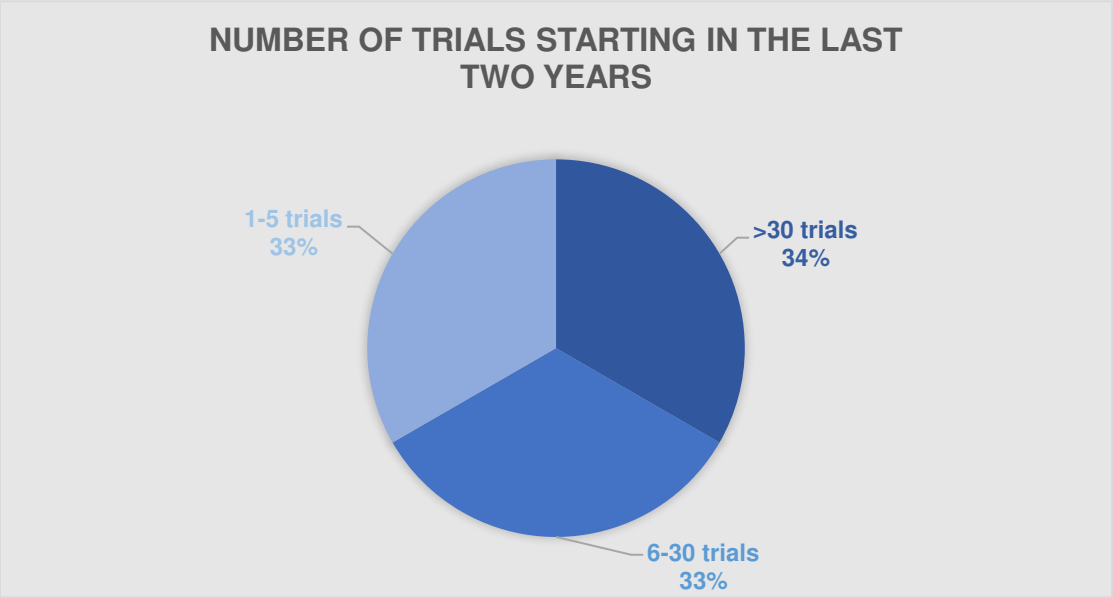


Figure 12 – Results of the survey's question "How many clinical trials have the clinical research site initiated in the last two years?".

These results indicate that the surveys' answers represent a heterogeneous sample of clinical research sites regarding their level of experience in clinical trials' conduct.

Among the trials that were initiated in the last two years, sites have also been requested to indicate the percentage of those clinical trials by type of intervention [Figure 13].

The results showed that most Portuguese sites deal with clinical trials with medicinal products, representing a median value of 95% of all clinical trials conducted at the site. Only five sites do not follow this trend, with higher percentages of trials conducted with medical devices (two sites) or other interventions such as nutrients, cosmetics or behaviours (three sites).

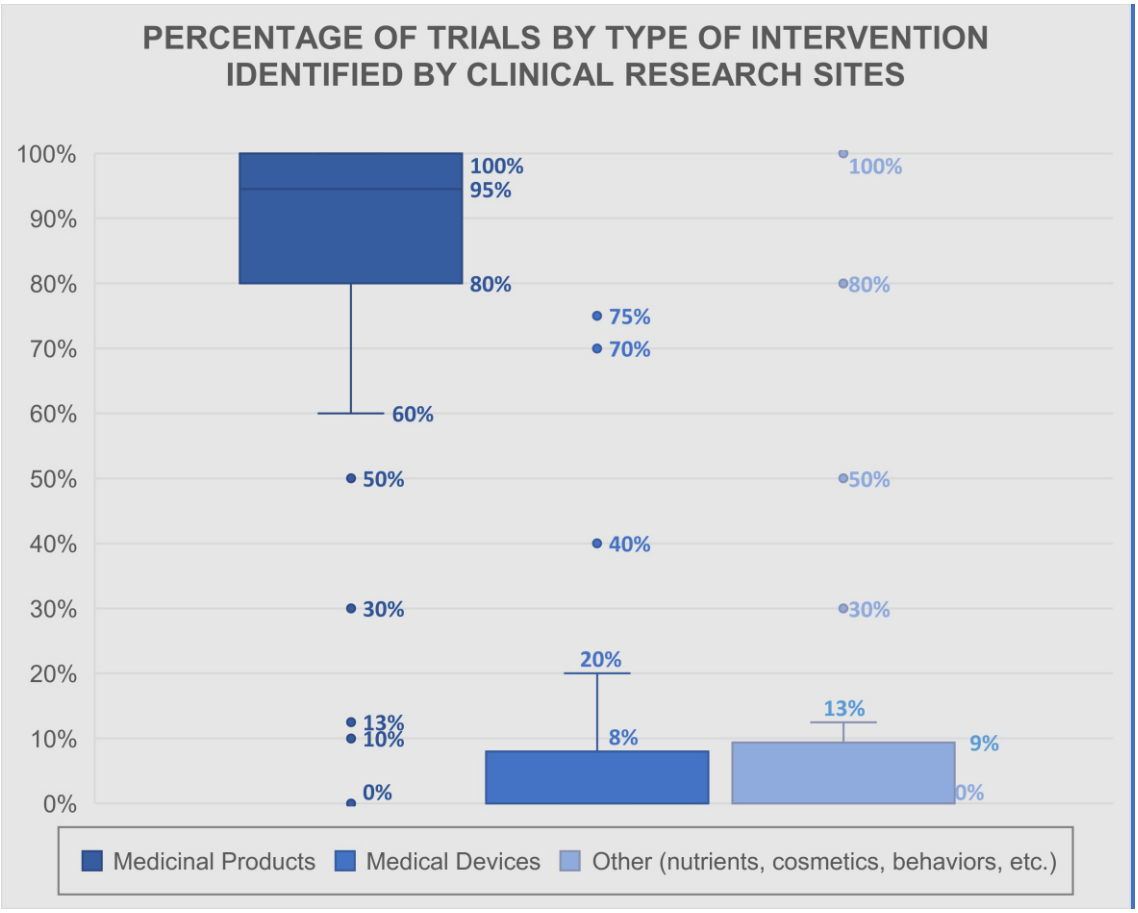


Figure 13 – Results of the surveys' question "Considering the clinical trials in which the clinical research site participated in the last five years (all studies active during this period, even if previously started), indicate the approximate percentage of studies of each type of intervention."

ii. Current use of tools to manage risks

Sites were questioned about the use of systematic tools to support the identification and evaluation of the risks at the site level. The survey's results were unexpected, with most sites (57%) affirming having a tool for this purpose [Figure 14].

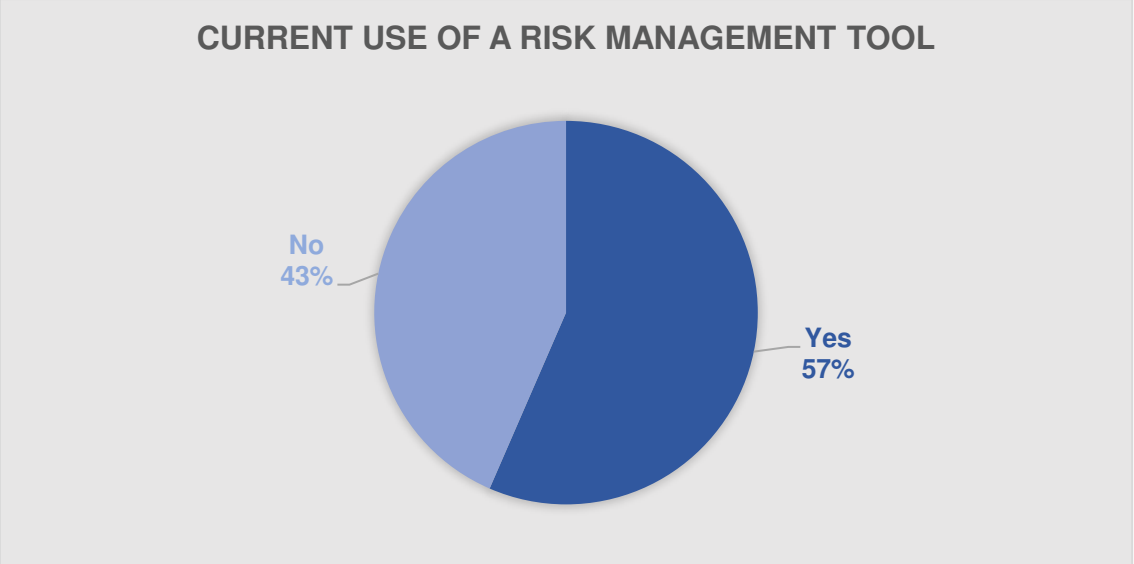


Figure 14 – Results of the survey's question "Does your clinical research site use any systematic tool to assess trial feasibility and trial-related risks identification and evaluation?".

To explore further these surprising results, answers to the question "Describe briefly the tool or procedure used" were analysed. The answers received were grouped and summarised in Table 2.

Table 2 – Results of the survey's question "Describe the tool or procedure used briefly".

RISK MANAGEMENT STRATEGY INDICATED	NUMBER OF SITES
Protocol analysis by PI and/or CRU to identify suitability, but no tool used to systematise or document the assessment	15
Use of a checklist or questionnaire to support the risk identification	6
Use of a systematised risk analysis tool	3
Not specified	2

This analysis revealed that most sites do not have an actual standardised tool or process to analyse the risks at the site level systematically. Most sites described that, based on the trial protocol, the Principal Investigator (PI) assesses the eligible population and the participants' safety risks. Besides, and supported by the CRU staff, they also assess the required equipment, materials, and staff availability. Some sites also mentioned the analysis of the competitive trials and the trial's logistical aspects, such as the collaboration across several departments or with external parties.

However, it was noted that this analysis is not focused on prioritising and preventing risks but rather communicating the identified limitations to the sponsors. The final objective seems to be that the sponsor can decide about the sites' participation and take ownership to control those risks.

It was also observed that sites do not systematise or capture the identified risks in a document or database that can support similar analysis in future. In summary, these answers revealed that the process is not optimised and needs to be fully re-started for each trial, wasting the staff time and efforts.

Only six sites declared to use a checklist or questionnaire to support the identification of critical aspects of the trial during the feasibility process. However, the analysis of these risks and their treatment was not mentioned for any of those sites. Among these six sites, one confirmed that, as part of the questionnaire's completeness, the impact of the trials' activities on the standard clinical practice is assessed.

Three other sites stood out for mentioning a broad focus on risk management procedures. Among those, one site referred that the initial analysis is reviewed periodically or once a new relevant risk is identified; another site confirmed the use of a risk management procedure that includes the risk evaluation, control, communication and revision. Finally, one site named a risk assessment tool capable of generating a structured report as the standard procedure.

After this detailed analysis of the results, it was concluded that only nine sites, among all the sites inquired (20%; n=46), have at least a support checklist or tool to assess trials' concerns systematically. Risk prioritisation, based on its probability and impact or any other risk management methodology, was not

mentioned by any site. However, some sites probably use such a methodology as the question was not targeted to assess this issue.

Based on the incongruence between the answers to the questions "Does your site use any systematic tool to assess trial feasibility and trial-related risks identification and evaluation?" and the description of the tool used, a reflection was done. It was pointed out the possibility that the question was not clear enough or sites do not realise that a standardised risk management tool can be developed and used.

It was expected that professionals who coordinate and oversee the clinical trials' activities, such as the Clinical Research Coordinators, will be more likely to identify the lack of a standardised procedure to anticipate and manage risks. In line with this premise, the possible relationship between the respondent's role and the answer regarding the use of a systematic tool has been explored further. However, no significative differences were observed (p=0.887) [Figure 15].

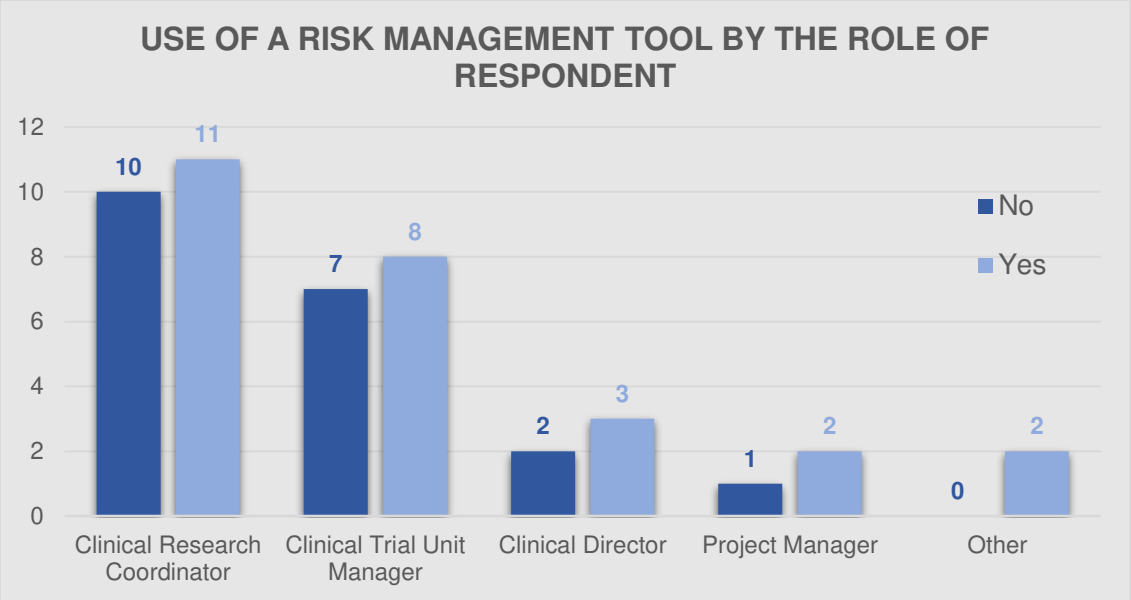


Figure 15 – Association between the survey's respondent's role and the confirmation regarding the use of a systematic tool to assess risk management.

Additionally, and based on the hypothesis that sites with a higher number of clinical trials are more likely to have standardised procedures, the association between the use of a risk management tool and the number of clinical trials initiated in the last two years was also examined. However, again, no association

was found between these two variables (p=0.397). This result indicated that sites with a higher number of clinical trials, and consequently more accumulated experience, do not strictly translate into better implementation procedures to manage risk.

The reasons for using a standard tool were questioned to better understand the sites' motivations [Figure 16]. Among the sites that confirmed the use of a tool, the most common reasons indicated were the anticipation of possible difficulties, the guarantee of patient safety and the allocation of the required staff.

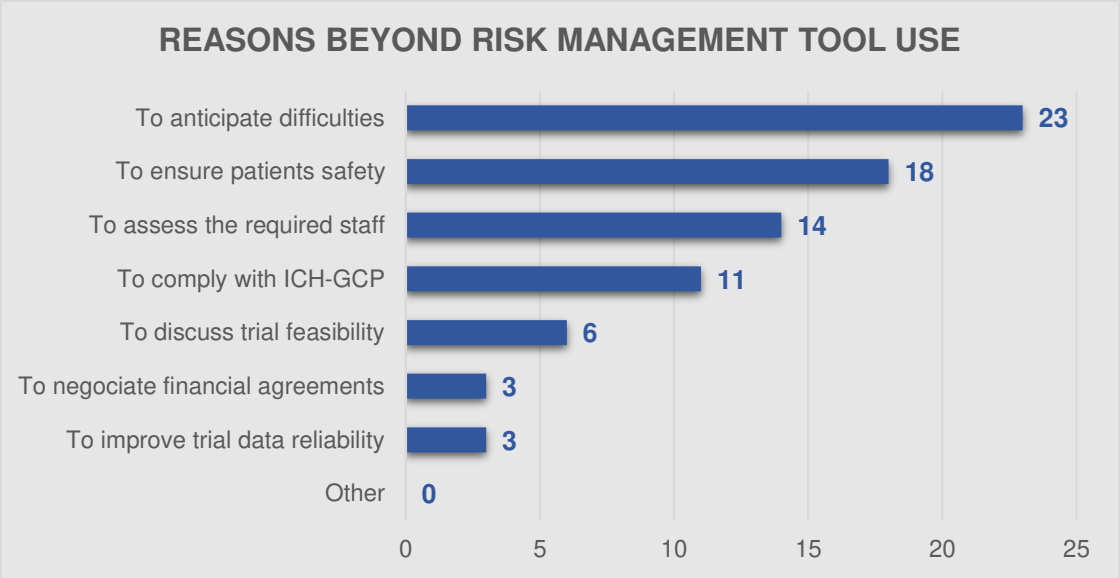


Figure 16 - Results of the survey's question "Indicate the reason(s) for which the clinical research site or study teams use this tool or procedure? (select the three options that apply the most)".

Similarly, the rationale was also asked to those who do not use a tool [Figure 17]. The most common reason was the lack of experience in performing a risk analysis, followed by the tool's anticipated complexity. To rectify these weaknesses, a systematised and easy to use tool with the most common risks and suggested mitigation strategies clearly identified was considered useful for the sites.

The fact that sites' risk assessment is not an ICH-GCP requirement also seems to motivate the lack of a standardised procedure. Among "Other" option, sites provided additional reasons, for example, the nonexistence of defined procedures to perform the risk analysis or the lack of an available tool to do so.

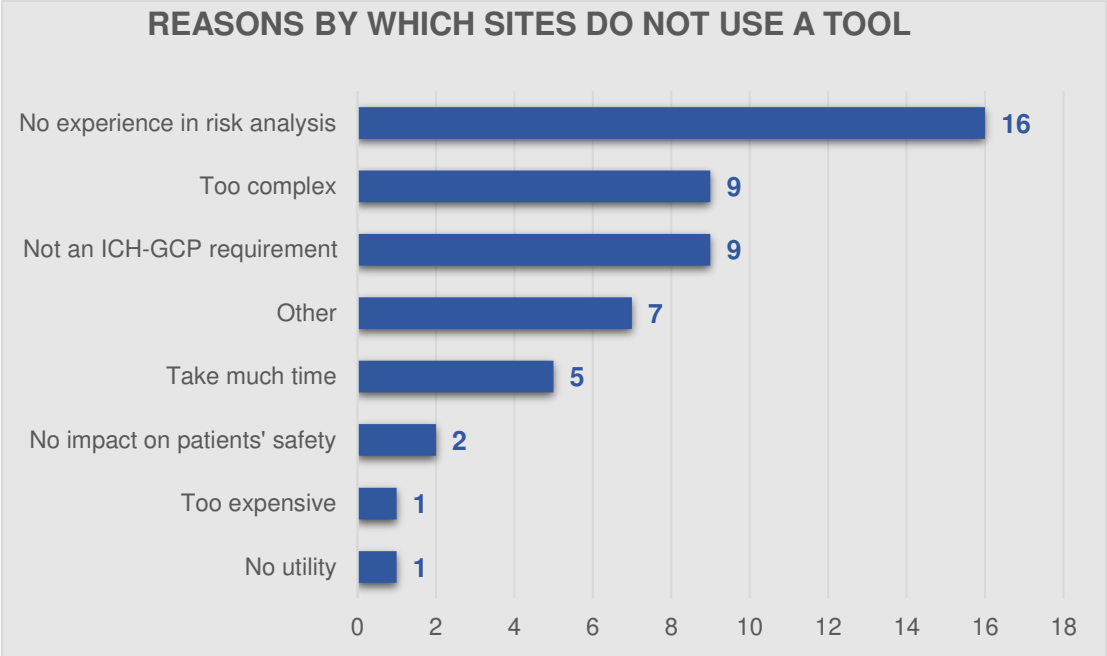


Figure 17 – Results of the survey's question "Indicate the reason(s) for which the clinical research site or study teams do not use a tool or procedure? (select the three options that apply the most)".

An interesting thought shared by three respondents is that they believe that, when a trial is received at the site, the most relevant risks and actions to prevent them have been already identified and implemented. This belief lay on the argue that sponsors, ethics committees and regulatory bodies have already addressed the trials' risks before the site effectively enter into action. Although these parties indeed assess and manage the trial risks, they have no accountability for the sites' processes. Therefore, sites need to ensure they control risks at the site level. This is a dangerous assumption as it can prevent sites from taking actions in advance. It can also lead sites to have completely different approaches to the same risks across different trials because the procedure becomes strictly dependent on the sponsors' recommendations.

One of the sites identified that sponsors generally provide sites with a very short time to feasibility activities which do not allow the conduction of a proper and profound feasibility process. It was also referred that there is a lack of institutional maturity that, although using tools with a similar purpose in clinical practice for assessing patients' safety, it is not capable of adapting such tools to the context of clinical research.

iii. The most common risks identified

Sites were requested to reflect on the most common risks they can identify in their trials' conduct [Figure 18].

Figure 18 – Results of the survey's question "What risk(s) do you identify in your clinical research site that could compromise the application of ICH-GCP and the performance of the clinical investigation teams in a clinical trial?"

Clearly detached from all other options is the lack of time of investigators and investigational teams. The staff's availability to perform the trial-related tasks will undoubtedly impact the quality of those activities, increasing the probability of almost every identified risk to occur. The staff is probably wasting too much time with repeated and administrative tasks which can be harmonised and centralised in the CRU. Additionally, sites can also be spending unnecessary time solving and managing issues that could be prevented in the first place by anticipating them.

The proposed tool is intended to reduce time constraints by helping sites work on their inefficiencies and decreasing the time spent on pointless tasks. Therefore,

sites can direct their efforts and time to the activities that effectively will bring the most valuable results, consequently improving staff and sites' performance in clinical trials.

Another result that should be highlighted here is that one-fourth of the respondent sites identified the recruitment below expected as one of the three most common risks across their trials. This result can indicate that sites are not able to provide accurate recruitment expectations to sponsors. The reason behind this could be related to the inexperience in considering withdrawals or refusals factors or analysing the eligibility criteria carefully. However, it can also be related to the lack of tools such as national or local databases that joint patients' information and allow a quick and realistic evaluation of the existing population against the protocol's eligibility criteria. This weakness is in line with the APIFARMA study published in 2019[9] that had already pointed it out.

Apart from the risks presented in the question's options, other additional risks were identified by sites, such as:

- failure to retain participants in the study by non-compliances related to the protocol-related assessments,
- inefficacy of articulation with third-party vendors contracted by sites, for example, those provided support on imaging assessments.

iv. Willingness to use a risk management tool and its characteristics

Throughout the survey, the respondents were impelled to reflect on their attitudes towards risk management. After this reflection, sites were finally asked if they would use a tool specifically developed for clinical research sites to facilitate the risk assessment and analysis at the start of the study and continuously during the study.

Results have shown that 87.0% of the sites inquired are willing to use such a tool, while only 4.4% refusing the use of the tool and 8.7% answering "Maybe" [Figure 19]. From this last group, sites argued that they are willing to use the tool if it demonstrates practical utility and applicability to the daily tasks.

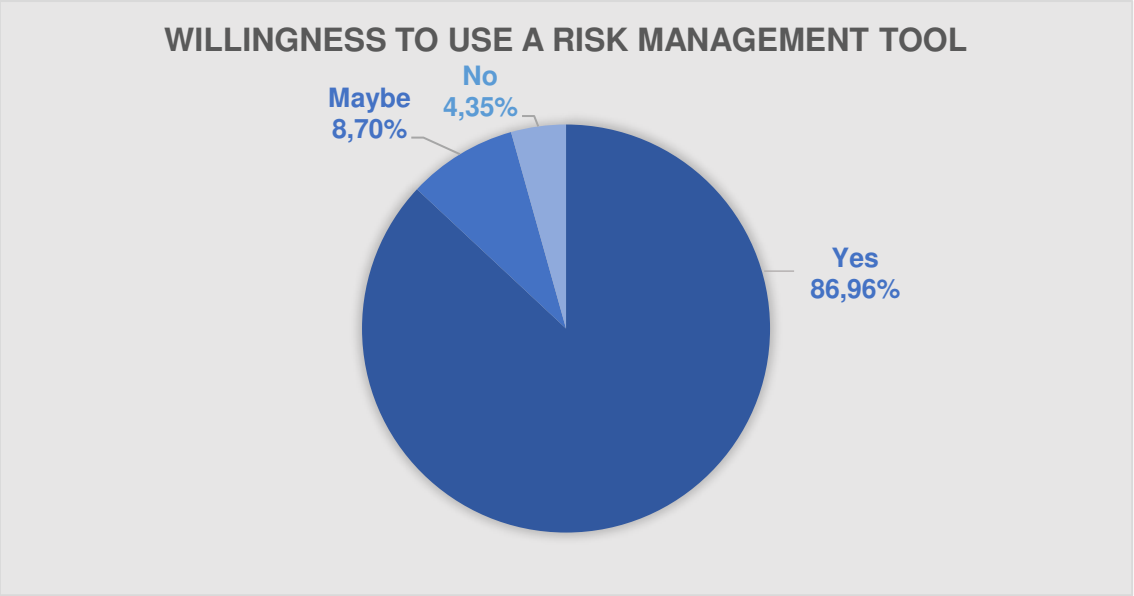


Figure 19 – Results of the survey's question "In your opinion, would the clinical research site or study teams use a risk management tool?".

The last survey's question intended to define the characteristics and features that clinical research sites valuable most in a tool to support risk management at the site level. Their preferences were ranked according to a 3-point scale from "Less Important" to "Very Important" [Figure 20].

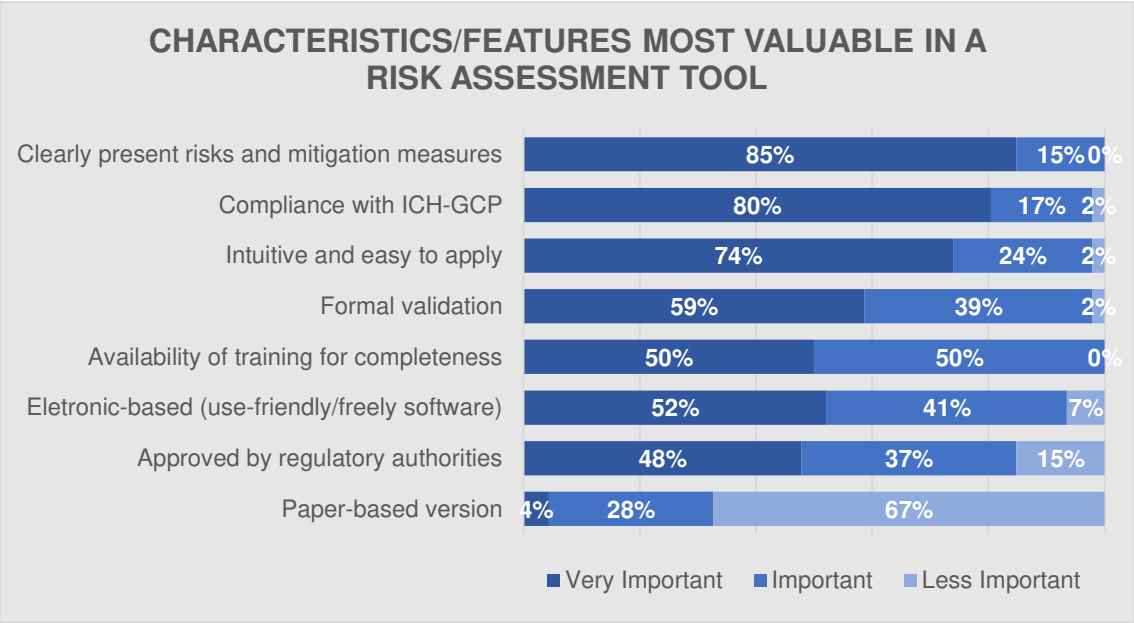


Figure 20 – Results of the survey's question "How important do you consider the following characteristics/features for a risk assessment tool?"

"Very Important" was the most common classification for all the pre-defined characteristics/features, except for the availability of a paper-based version that was considered as "Less Important" by most sites (67%).

Among the most important characteristics/features identified, the clear identification of risks and mitigation strategies was highlighted. In line with this, the developed tool incorporates a collection of usual risks and suggested mitigation measures. It also identifies possible root causes that can underpin sites in the investigation of different management strategies.

Sites also suggested other features they considered important to be incorporated into the tool. Some examples are the easy adaptation to different therapeutic areas and type of intervention, the quick application and maintenance, the assurance of data protection, the standardised use for all clinical research sites, the reduced analysis subjectivity and the support for internal audits. All these suggestions were covered by the developed tool.

However, although they have been considered during the tool development, some other suggestions were not incorporated and were identified as future research:

- integration of the tool within a broader risk management process and the quality management system of the institution;
- definition of quality tolerance limits associated with each risk to facilitate deviation detection and application of target measures;
- demonstration of utility by a validation process based on a real scenario.

The first two suggestions were not implemented as it was considered the lack of sites' experience in risk management activities. Therefore, and although these insights are very pertinent, it was decided to keep the tool as simple and easy to use as possible. The development of a more complex tool may be further explored as long as the experience in risk management methodologies is improved. Finally, the last suggestion was not executed under the scope of this work due to time constraints.

Risk Management Tool

The risk management tool developed in the scope of this research can be consulted in Appendix D.

i. Final version of the tool

The final version of the tool is a Microsoft Office Excel-based file. Beyond the spreadsheet where the tool is available, it also includes the following:

- **Instruction for Use**, where the instructions for the tool completion and the list of abbreviations are provided.
- **Process Overview**, where the flowchart with the suggested process is presented.
- **References,** where the references mentioned in the risk management tool spreadsheet are detailed.
- **Coding**, where data used to support pre-defined drop-down lists and formulas used in the tool is available. This spreadsheet is hidden and locked to edition to avoid misconfiguring the tool's programming.

Focusing on the Risk Management Tool spreadsheet, a header for protocol identification is available, including the identification of protocol code/name, date of initial assessment and date of the last update.

As Excel does not allow an audit trail, it is advisable that before any change, the tool is duplicated to a new Excel tab, renamed with the date of assessment and completed in the new tab. It is also suggested that cells that suffer any change from the previous assessment are coloured in grey, so collaborators can quickly identify the changes from one version to another.

The tool is constituted by the following columns:

- **Category**: seven categories are pre-defined in the tool. However, additional categories can be added or the existing ones omitted according to the specific sites' needs.

- **Identified Risk**: forty risks are pre-defined in the tool. However, additional risks can be added or the existing ones omitted according to the specific sites' needs.
- **Probability**: allows the selection of one of the three pre-defined options – Rare (1 point), Possible (2 points), Almost Certain (3 points) – from a drop-down list. A colour-coding automatically applies according to the option selected: Rare is coloured in green, Possible in yellow and Almost Certain in red [Figure 21].
- **Impact**: allows the selection of one of the three pre-defined options – Minor (1 point), Moderate (2 points) or Major (3 points) – from a drop-down list. A colour-coding automatically applies according to the option selected: Minor impact is coloured in green, Moderate impact in yellow and Major impact in red [Figure 21].
- **Total Risk Score**: based on the option selected in Probability and Impact columns, the cell automatically calculates the product of the two values and returns the overall risk score, according to a three-point scale of Low (less than 2 points), Moderate (3 or 4 points) and High (more than 5 points). A colour-coding automatically apply according to the total risk score: Low risk is coloured in green, Moderate risk in yellow and High risk in red [Figure 21].

		PROBABILITY		
		Rare	Possible	Almost Certain
IMPACT	Minor	1	2	3
	Moderate	2	4	6
	Major	3	6	9

Figure 21 – Risk Assessment 3 X 3 matrix. The colours represent the risk score: green coloured boxes mean low risk, yellow boxes means moderate risk, and red boxes means high risk. Source: Chartered Institute of Management Accountants.

The colour-coding allows the user to have a visual understanding of the risk analysis results.

- **Potential Causes**: presents a list of possible causes for the identified risks.
- **Potential Controls/Mitigation Actions**: presents a list of possible controls and mitigation actions for the identified risks.
- **References**: shows the bibliographic sources used for the identification of causes and/or controls. Detailed references' information can be found in the spreadsheet "References".
- **Responsible**: allows sites to enter the name of the person or group of people accountable for controlling and mitigating the risk.

In the final version of the tool, the categories initially defined in the methodological phase were adapted to match the final list of risks chosen to be included. The following changes were performed:

- "Safety" category was deleted. According to ICH-GCP (R2)[1], the investigators' responsibilities regarding subjects' safety are mainly: 1) ensure that adequate medical care is provided for any adverse events, and 2) report such events to the sponsor according to the reporting requirements and within the specified timelines. As identified risks within this category were only related to the safety reporting responsibilities, those risks were integrated into the category "Data Collection".
- "Complexity" category was renamed. It was considered that the name of the category is too broad and did not intuitively suggest its scope. Therefore, "Study-Specific Procedures" replaced the previous category name. This category includes risks related to procedures required by the sponsor for a specific trial regardless of its complexity, such as, but not limited to, uncommon procedures beyond the usual standard of care, multiple vendors, collection of lab samples, management of sub-studies or blinding requirements.
- "Subject Population" category was renamed. It was considered that the name of this category could limit the discussion to the risks associated with the recruitment only. Therefore, the category was renamed to "Subject Recruitment and Retention" and includes risks related to the eligible population identification, recruitment, retention and withdrawal.

- "Staffing, Supplies & Equipment" was split. Due to the high number of risks identified within this category compared with the other ones, and also because staff management is a key point for trials' success at the site, two different categories were considered:
    - "Staff qualifications and training" focus on risk related to site staff's availability, qualifications and training and,
    - "Facilities and Supplies" including risks related to the adequacy of facilities and the suitability, maintenance, calibration and storage of trials' supplies and equipment at the main investigational site or any satellite site, such as those used for complementary diagnostic tests and therapies.

The three other categories defined in the methodology remain without changes in their name or scope: "Data Collection", "Investigational Product", and "Essential Documents".

In Table 3, the list of risks included in the final version of the tool is presented. These risks were chosen based on the potential for prevention or mitigation at the site level, either by implementing new processes or introducing changes to the current processes.

Table 3 – List of risks included in the risk management tool.

Data Collection
Safety reporting fails to meet the required timelines
No restrict access to the Electronic Health Records System by the sponsor's representatives
Delay in data entry/query resolution
Delay in EDC signature by PI
AEs not adequately documented in source documents
Missing source documents or lack of document specifying the location of source data

Essential Documents
New safety information not available for all the required study team members
Incomplete/Incorrect site personnel signature log
ISF is not ready for inspection and relevant documents were either not filed, or filed late, or located outside the ISF structure
Patient File not completed/completed late
Relevant correspondence not archived in ISF regularly
Delay in CV collection
Delay in contracts signature by PI or Board of Directors
Facilities & Supplies
Oversight deficits due to multiple vendors participating in a trial
Delay in assessments performance (for example, imaging examinations)
Vendors delays in the transfer of data and query resolution
Lack of communication among participating departments at site
Miscommunication with central vendors contracted by the sponsor
Change in facilities or equipment suitability
Study assessments performed by an external vendor
Investigational Product
Investigational product stock is not adequate
Storage requirements not met for investigational product
Temperature Excursion not noticed/reported
Wrong kit dispensed to a participant
Multiple studies using the same storage place at the site
Staff qualifications & training
PI unavailability
A study requires clinical trial naïve investigators
High turnover of study team members
Staff inadequately trained

Study-Specific Procedures
Blinded personnel receive unblinded data
Handling requirements for study samples not met
Increased complexity due to multiples sub-studies
Network connectivity issues do not allow for ePRO device fully working
Study Visits performed out of the required window per protocol
Subject Recruitment and Retention
The study allows the inclusion of vulnerable populations (children, inmates, mentally ill)
The study allows the inclusion of women of childbearing potential
High number of consent withdrawals
Informed Consent / Reconsent process fails to meet regulatory requirements
Recruitment expectations not met
Delay in the participants' reimbursements

Following the identification of the risks, sites can complete the risk analysis based on probability and impact determination, and overview the total risk scores. Considering the available time, the risks with the highest scores (high risks coloured in red) should receive priority treatment through targeted monitoring and mitigation, followed by moderate and then low-risk scores. All risks should be reviewed periodically; high risks with more frequency.

Sites can consult columns concerning possible causes and controls and use the recommendations provided in the tool as a starting point for further discussions on risk treatment.

Table 4 shows, as an example, the suggested causes and controls for three of the most common risks identified in the survey by respondent sites.

Table 4 – Potential causes and controls for three risks identified in the tool.

IDENTIFIED RISK	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS
PI unavailability	• PI is participating in several studies. • PI accumulates other roles within the site.	• Have the PI's availability into account during the feasibility and site selection phase and proactively suggest other PI than the one indicated by the sponsor (consider investigators with less clinical research experience and provide the rationale to sponsor). • Have a less experienced investigator accompanying the PI-specific activities closely.
Recruitment expectations not met	• I/E criteria are very specific. • Patients diagnosed/treated at a different department not included in the study team. • Recruitment expectation provided is not realistic.	• Confirm if the protocol allows for subject rescreening. • Discuss the patient pathway with the hospital (which medical speciality does the diagnosis; which medical speciality can prescribe the treatment, etc.). • Liaise with patient representatives and colleagues from different hospitals to let them about the study. • In the Department meeting, remind that a trial is ongoing and recruiting for patients with these eligibility criteria, so the other investigators are aware of them and let them know about the recruitment status.
Delay in contracts signature by PI or Board of Directors	• PI is not available to sign/date on time. • Contract takes too long to be sent from the PI's department to the Board of Directors. • Board of Directors takes a long to sign the contracts. • Board of Directors does not define clinical research as a strategic priority • Board of Directors has limited time	• Ask sponsor if the electronic signature is acceptable • Agree with the Board of Directors upon a common and well-established pathway for contracts negotiation and signature for all clinical trials. • Be informed about the upcoming Board's meetings and agreed with them on the timeline to have the contract signed based on these dates. FUP after meetings; • Define with Board and sponsor if the electronic signature is acceptable; provide training in the use of electronic signature through the Citizen Card application freely available. • Agree with the Board of Directors to delegate a member to sign the contracts on behalf of the President/ Board of Directors.

ii. Recommendations for the tool's use

As mentioned previously, this is not a static tool. Its software, Microsoft Office Excel, allows a flexible and dynamic utilisation. For this reason, the tool can easily be adapted to any kind of clinical trial regardless of the intervention – medicinal product, medical device, surgical technique, nutrition, behaviour, among others. Although it was not developed with this objective, the tool can also be applied to non-interventional studies as long as it is adapted to this framework, probably with less identified risks but yet functional.

This tool and its content intend to be used as a starting point for discussing risks and their controls. It is recommended that a multidisciplinary discussion involving different roles within the site takes place. The risk management process described below is projected to be more agile and intuitive if the tool is being used as a regular procedure and is well-known within the site across all the functional groups.

It is recommended that the first tool's completion is done during the feasibility phase, when a new trial is proposed to the site. It is suggested that the CRU is familiarised with the tool and the trial protocol before its first utilisation. The tool should be adjusted based on the knowledge about the protocol and the trial requirements regarding staff, facilities, equipment, and population adequacy. This adaptation can be made either by adding new risks or categories or by deleting some pre-defined ones. Then, the risk analysis should be completed by the CRU according to the probability and impact assessments and based on the previous experience with similar trials.

After this draft completion, the CRU should meet with the PI and other staff as necessary, such as radiologists, nurses or pharmacists. This meeting is intended to gather input regarding the suitability of the site to perform a given trial. Based on this feedback, the risk analysis made previously by the CRU may have to be adjusted. Also, some additional risks can be identified during this discussion, and their inclusion should be considered.

After this revision, a final decision should be made regarding the acceptance to participate or not in the trial. At this phase, and based on the risks with the highest scores, the site can introduce some alternatives to overcome major risks with the

sponsor. For example, suppose it is detected a high-risk regarding PI availability during the feasibility assessment. In that case, the site can reach the sponsor to present a different PI suggestion and provide them with the rationale.

In case the sponsor chooses the site to conduct the trial, and before the Site Initiation Visit (SIV) is performed, the tool should be revised. At this phase, it is also valuable to add or delete risks established previously as the knowledge about the protocol and sponsor requirements is now broader. This new analysis should be, again, discussed with the PI and the applicable staff. The results will allow the site to implement some preventive actions before the trial even starts. At the SIV, these results can also be discussed, and a sponsor's support can be requested as necessary. This proactive discussion will show the sponsor the site's commitment to the trial.

The primary CRC should be accountable for maintaining the tool updated and ensuring that the responsible parties implement control measures. The CRU should keep oversight of all trials' risk analysis to optimise procedures common to several trials and ensure efficient resources allocation.

After the study initiation, it is still important to periodically revise the tool. The team should agree on a timeline for the tool revision depending on the study development stage. For example, during the recruitment phase, the tool can be revised more often than during the phase patients are in treatment or follow-up. These ongoing revisions will allow the site to manage risks continuously, so the resources and efforts can be targeted to the most critical processes at each point. Revision is also essential as secondary risks can be identified as, for example, risks resulting from the implementation of a mitigation action.

The tool completion in each of the recommended timepoints should follow subsequent steps:

1. **Complete and/or edit "Identified Risk" and "Category" columns**:
   Firstly, the site should focus on the identification of risks that better suits a given trial. The CRU can create a list with all risks that are being identified across several studies (for example, by adding a new spreadsheet to the Excel file). With the increased use of the tool, it will be easier to have a list

from where previously identified risks can be picked. In this way, the cumulative experience and knowledge are not wasted.

2. **Complete risk analysis – "Probability" and "Impact" columns**:
   Based on the pre-defined 3-point scale, the site should select the most appropriate classification for the probability of the risk to occur and the magnitude of its impact should it occurs. This analysis will become more accurate as long as the site collects and maintains data to support this assessment. For example, the number and nature of issues that occurred in previous trials will allow a more accurate probability assessment for similar risks in future trials; similarly, the data concerning the consequences of past issues can be used to support the impact assessment.
3. **Reflect on total final risk scores**:
   After obtaining the scores for each risk, the site should look to the risks with higher scores and decide on avoiding, eliminating, transferring, accepting or treating each risk. For example, suppose there is a risk of a specific trial assessment is not completed within the required timelines. In that case, the site can decide to transfer this risk by contracting an external clinic to perform the required assessment. This decision should be multifactorial and multidisciplinary and, as for all other steps, it will be most adequate as long as this evaluation process is becoming usual.
4. **Discuss the root causes and mitigation plans**:
   Only after choosing the risks that will require treatment, the columns "Potential Causes" and "Potential Controls/Mitigation Actions" should be addressed. This means that these columns are not intended to be completed for every risk but rather for the most critical risks identified. In this way, it is ensured that the efforts are being applied to the areas that really matter for each specific trial. Several analysis strategies can be used for this purpose as brainstorming sections, cause and effect diagrams, among others. Additional methods and tools can be found in the ICH guideline Q9[73] on quality risk management.
   Although several methodologies are available, they usually are based on similar assumptions. Firstly, the team needs to think about the root cause that can lead a risk to occur, i.e., to become an issue. The recognition of

underlying causes will support the identification of actions to minimise the probability of occurrence and/or its impact on the participants' safety and trial data. These mitigation strategies need to be aligned with the site objectives, the available resources and the sponsor requirements.

This suggested process is summarised in Figure 22 to better understand the responsibilities, methodologies, and tasks recommended at each phase of the clinical trial implementation at the site.

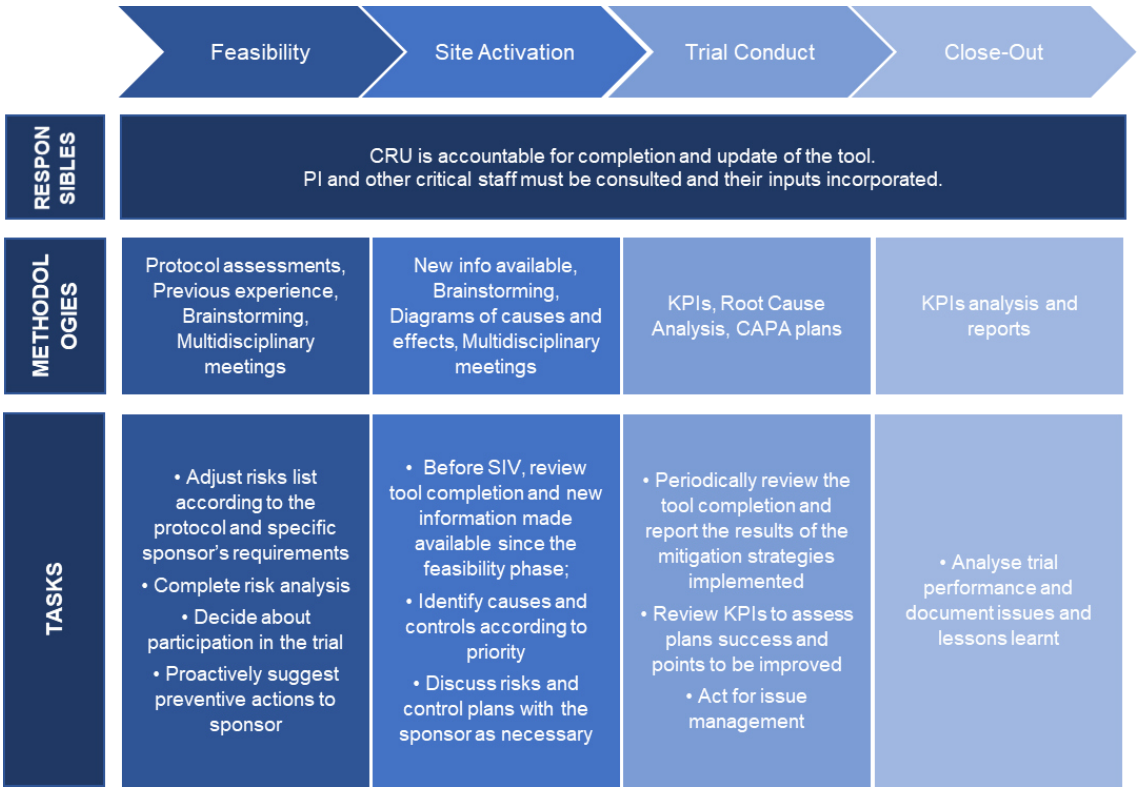


Figure 22 – Suggested process to implement the tool within the clinical research sites.

After implementing mitigation actions, their effectiveness should be monitored so the process can continue or change. At the time of the review, the site and team have already accumulated new knowledge and experience that will be used to improve the mitigation plan.

An easy and simple way to review and monitor the performance is to establish Key Performance Indicators (KPI) and corresponding thresholds. Detection of deviations from the predefined limits should trigger an immediate evaluation to determine if action is needed.

This methodology is often used by sponsors to compare performance between sites within the same trial and across different trials. These data are not only used to track the performance during the study participation but also to support the decision on future collaborations. A recent paper by Carvalho et al. (2021) affirms that most Portuguese CRUs have KPIs already defined, while in some less mature CRUs, the process of defining the KPIs is still ongoing.

This process starts with setting a few KPIs by the site according to their context and objectives. For each KPI are then defined threshold criteria that trigger different levels of risk. Table 5 presents two examples of possible thresholds to be established by the sites. It is necessary to note that, for the same risk, the thresholds may have to be adapted based on the sponsor's requirements or trials' specifications. Although the proposed tool does not incorporate these thresholds, it can be used to help sites in defining them.

Table 5 – Examples of thresholds criteria for risk assessment. Source: TransCelerate[65].

Identified Risk	Low Risk	Moderate Risk	High Risk
Delay in data entry/query resolution	≤ 5 days after the subject's visit	6-10 days after the subject's visit	> 10 days after the subject's visit
Recruitment expectations not met	Average enrolment rate per month is at least equal to the expected	Average enrolment rate per month is lower than the expected, and recruitment period just started	Average enrolment rate per month is lower than the expected, and recruitment period is about to close

However, this methodology demands a higher alignment of sites with the risk management mindset as sites must have the ability to collect and organise data. These data will support the calculation of average performance to allow comparisons between trials or CRCs, but also to monitor and control the site performance during the trial. The collected data and indicators should be well documented and reported within the organisation to the CRUs' Responsibles and from them to the senior management as the Board of Directors.

KPIs are not intended to be directly communicated to sponsors. However, as sponsors also use similar KPIs to monitor site performance in their trials, they will note an effective improvement. This process is then a great way to improve the sites' reputation among clinical research stakeholders and, as a result, attract more trials and investment.

iii. Impact of the tool implementation

Benefits of the risk management tool

Among the direct benefits of this tool implementation, it is the increased understanding of each project, which leads to the preparation of more realistic plans and attention reallocation to the projects that need it more. Because the risk analysis in the tool is based on a risk matrix, it allows a visual summary of the various risks and the perception of their different urgencies, facilitating the communication about risks within the team.

The increased communication about the common challenges may create a closer and more positive working relationship because each team member will feel they contribute directly to the trial's success. The feeling to be part of a team and contribute to delivering better results can motivate them to work with a focus on productivity. The team's involvement during the risk management process is essential to give them the autonomy to play an important and active role within the whole process. Team members need to know that their success will directly impact the team's success and, consequently, the trials'. This change in the team's mindset will also impact the clinical research site and the healthcare institution's reputation.

With risks being actively tracked and managed, the tool seeks to help the team to maintain a focus on the highest priority areas and outcomes, preventing problems from being overlooked but efficiently treated. The tool's application to several studies also permits that recurrent issues or trends that are usually not detected are noticed earlier and trigger earlier actions as well. For example, suppose by analysing the risks of several trials, it is observed that the ICF process is classified as high risk for most of them. In that case, CRUs' managers or other decision-makers know that this process will need attention. In this example, the

CRU can allocate a team to address this common risk holistically, leading to the implementation of measures at the site level. This can be executed through a standardised procedure applied to all their trials that, once implemented, will have the ability to minimise this risk across all trials affected. In this way, resources and time are saved by not having several people working on minimising this risk for each trial.

The tool also provides leadership with better quality data, enabling them to make more grounded decisions based on the CRU's specific reality and in their trials needs. Information gathered from the tool is updated as it is collected in real-time, as risk management methodology requires. Therefore, CRU's collaborators and investigators can ensure that their decisions are better informed, based on the lastest available data and targeted to the highest priority areas.

It is expected that institutions will be less likely to receive warnings for non-compliances either throughout the inspections conducted by regulatory authorities or external audits by sponsors or their representatives. Although it is impossible to eliminate the risk, the tool will be important to demonstrate to inspectors and auditors that issues are not due to a systemic failure, and the site has measures in place to analyse and prevent such problems.

This risk management methodology at the site level will also contribute to subjects' safety in the trial. As sites are the first level of interaction with trial participants, implementing a risk approach to the site processes can prevent immediate harm to the participant. The sponsor can also obviously put measures into practice, but, in most cases, the issues with subjects already occurred, and the sponsor can only help the site set measures to prevent the issue from reoccurring. For example, suppose an expired kit is assigned to a participant by the site because there is no standardised process in place to confirm the expiration date at the Pharmacy. In that case, the sponsor can act to have the participant return to the site to receive another kit. However, if the site had identified this risk upstream and had implemented measures to control it, the subject would receive the correct kit at the beginning.

Summarily, early awareness of potential problems means that the right people can intervene to mitigate an issue before it becomes too severe to do anything about it. The shift from a problem-solving culture to a preventive culture will also

allow saving money. With efficiency improvements, sites will become more attractive for research investment. As explained in the Background section, more clinical trials mean more patients participating in trials, which means that the healthcare institution will not have financial charge related to these patients' care. Savings from medical appointments and examinations can be reinvested in clinical research or even in other priority services or areas identified by the administration.

Benefits of a risk management culture

Although the tool can have such benefits, it is not expected that the sites will grow their performance exponentially right after its implementation. However, it is intended that this tool can change the mindset of sites, especially CRUs, from a culture in which sites act after the issue effectively occurs to a culture of preventing or quickly mitigate its effects.

It is believed that this culture of risk management can excite sites to develop other tools and procedures to improve their performance continuously. Beyond the already suggested strategy to set and monitor KPIs, sites can also create Standard Operating Procedures (SOPs) for their critical processes, such as obtaining Informed Consent Form, Source Documentation or Monitoring Visits. For example, most sites' pharmacies usually have SOPs to describe the investigational product cycle, most commonly regarding medicinal products.

Sites should also have a process concerning internal audits, defining its periodicity, responsibilities and criteria to choose target trials. A suggestion is, for example, to have a CRC from another trial auditing the trial that it is not under his/her scope. The audit can focus specifically on the Investigator Site File (ISF) as this is a site's sole responsibility. Although the sponsor's representatives usually look at the ISF during the monitoring visits, according to ICH-GCP (R2), the sponsor's responsibility is to provide all the required documentation to the sites and not to ensure its proper management and storage. By gathering experience in this process, the audits can focus on other processes and check for compliance with the SOPs, for example, by verifying that certified copies are being done as described or the ICF process is being followed.

Another practice that may be implemented is issue management. This is the process by which sites learn from a past event and have the ability to apply these learnings to other trials. For example, when a risk cannot be prevented or avoided and occurs, this becomes an issue. The site should analyse the issue by understanding its root cause and establish a CAPA (Corrective Action and Preventive Action) plan. This process consists of a set of measures to correct the issue immediately and to avoid issue recurrence. For example, suppose there is a risk that temperature excursion is not reported and the root cause analysis indicated that the alarm was not triggered due to a wireless network. As a corrective action, the excursion must be reported immediately to the sponsor. Regarding the preventive action, the site can evaluate possibilities to connect the data logger to an autonomous network or have a back-up device that connects to a different network. In this case, the preventive action is useful for the trial in which the issue occurs, but it is also important to prevent this issue from occurring in other trials.

All these procedures and techniques are intended to strengthen the risk management culture and complement the proposed tool in identifying the site's inefficacies. These complementary methodologies will enhance the magnitude of the benefits already described for the use of the tool. Overall, there is a potential to increase sponsors' trust in the performance that sites can achieve while conducting their clinical trials and, consequently, attract sponsors to collaborate more often with the site.

iv. Limitations of the tool and future work

One of the limitations of this tool is the subjectivity of the risk analysis. The probability and impact assessments are very susceptible to the user's perceptions and beliefs. For that reason, a risk assessment for a given trial may differ depending on the person that is completing the tool at the site. As the tool intends to help sites in the identification of the priority areas for action, this subjectivity issue can be overcome by ensuring that the tool for a specific trial is completed by the same person or group of people. If different people analysed different studies, this subjectivity is not so critical as prioritisation within each trial is not biased by the other trial's assessment results.

Another limitation of the tool is the lack of robustness of the risk analysis methodology. The method chosen was as simple as possible to allow staff with little or no background in risk management to perform the analysis. However, this simplification of the risk analysis methodology also brings some constraints.

As a qualitative method, matrices are imprecise, and if the inputs and assumptions are incorrect or do not correctly represent reality, the results from the analysis are meaningless[74]. This could be improved by using a quantitative method that often provides more accurate results, as using numbers usually imply more precision in results, but is costly and time consuming[74]. Additionally, risk matrices do not provide the possibility to address the risks interactions and correlations[75].

In risks matrices, the quality of the results also depends on the quality of the available information. The absence of real data will lead the decisions about risks to be based on personal perceptions. Therefore, risks can be under or overestimated. Consequently, sites should make all the possible efforts to gather valid data to support the determination of the risks' importance.

Regarding the specific matrix used – 3 X 3 matrix –, the analysis provides only three groups for the risk categorisation, which could not allow enough differentiation between risks. For more experienced teams, it would be advisable that matrices with wider scales for both the probability and impact are used[75]. These additional levels would allow a more precise analysis, resulting in better allocation of resources and support to decision making.

The fact that this tool is not validated also constitutes a limitation. According to the survey's results, in a 3-point scale from "Less Important" to "Very Important", 59% of the respondents considered that it is "Very Important" to have the tool validated for use. Due to time constraints, the tool has not been validated. However, it is suggested a methodology to validate the tool through the conduct of a pilot testing in a small sample of the target population, i.e., clinical research sites [Figure 23]:

1. Definition of Indicators: a set of indicators should be established to measure the impact of the tool implementation within the sites. The indicators should be agreed upon by the consensus of a group of experts.

Sites will have to collect data to report those indicators, so it is essential that they participate in this consultation. The following indicators are recommended:

a. Time from contract ready to sign and contract fully signed;
b. Time from site activation to First Patient In (FPI);
c. Number of major protocol deviations;
d. Enrolment rate (real enrolment *vs* contracted enrolment).

2. Selection of testing group: at least two trials (at a maximum of 50% of all the sites' trials) should be selected to use the tool. For the included trials, some data should be collected to allow the stratification at the time of analysis. The trial phase, therapeutic area, sponsor (industry or investigator-initiated), PI, primary CRC, among other parameters should be collected. The site should make every effort to have heterogeneity in the testing group regarding those parameters to avoid biased results.
3. Selection of control group: the remaining trials not selected in step 2. will constitute the control group.

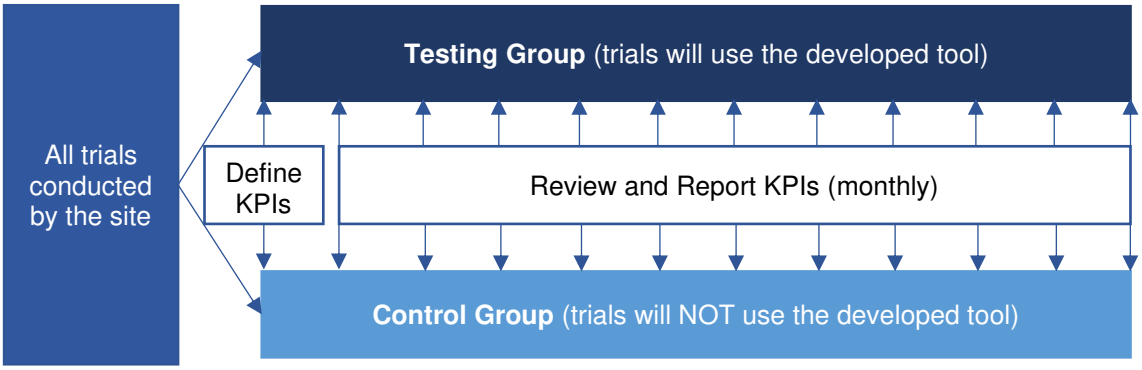


Figure 23 - Proposed validation process to the risk management tool.

To avoid contamination between the two groups, all studies of a given PI or CRC should be in the same group. For example, if a given PI is responsible for two trials and one of them is assigned to use the tool and the other one not, there will be a tendency to implement improved working methods in both trials.

4. Monthly review and report: For both groups, review and report of indicators' results should be done monthly. As a suggestion, the previous

month's results could be sent between the 1st to the 5th day of the following month.

It is suggested that indicators from both groups are analysed at least quarterly. The comparison between the two groups from the baseline assessment will allow concluding if the tool is useful to improve sites' performance. Additional comments to the tool should also be considered and, if applicable, incorporated in a new version.

6. Conclusions

Even though risk management is having considerable attention from the stakeholders in the last years, it was identified the need for a more in-depth assessment of the risks that may arise at the site level and the strategies that the clinical research sites can implement to mitigate them upstream.

This work provides an understanding of how clinical research sites can strengthen their contribution to clinical trials' success by adopting a more proactive role in the risk management of clinical trials' operations at the site level.

An overview of the current risk management practices in Portuguese clinical research sites was presented. The major conclusions of this analysis are:

- Most of the sites have already fully dedicated professionals to clinical research activities, and at least one third have a CRU for the coordination and management of clinical research activities;
- Most of the sites work on clinical trials with medicinal products, representing an average value of 95% of all clinical trials conducted at the sites;
- The most common risk identified by sites is the lack of time of investigators and investigational teams;
- One-fourth of sites confirmed recruiting below the expectations;
- Most of the sites do not have a standardised tool or process to systematically analyse and document the risks related to the clinical trials' activities at the site level;
- Sites with a higher number of clinical trials, and consequently more accumulated experience, are not strictly associated with the implementation of better procedures to manage risk;
- Almost nine in ten sites are willing to use a risk management tool to support their activities.

In line with these results, a risk management tool tailored to the clinical research sites use has been developed. It is a dynamic tool that can be easily adapted to any clinical trial regardless of the intervention type. It allows clinical teams to identify risks and prioritise actions and resources allocation based on the most

critical processes. The template developed intends to be a starting point for a multidisciplinary discussion about risks and how to manage them.

Among the tool's limitations are the simplification of the risk analysis methodology and the lack of validation. Therefore, future research is needed to improve the tool's performance.

From a broad perspective, this tool is expected to:

- Contribute to a higher alignment of sites with a risk management mindset;
- Excite sites to develop complementary tools and procedures to improve their performance continuously;
- Decrease the sites' dependency on the sponsor by encouraging a more proactive role in the clinical trials' risk management process;
- Enhance the overall clinical research sites' performance regarding clinical trials operations at the site level both in industry and investigator-initiated trials;
- Improve the sites' reputation among clinical research stakeholders.

In the end, these achievements may attract more investment for clinical research in Portugal, resulting in a higher number of trials and subjects recruited.

In conclusion, this work recognises that clinical trials involve risks that can affect the safety of human participants and the reliability of the clinical trial data. Therefore, a practical approach to improve trials' success is proposed. This success can lastly be translated into a benefit for patients and society.

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Appendix A – Survey

Perceção do Risco em Ensaios Clínicos

Os campos assinalados com um asterisco (*) são de preenchimento obrigatório.

Perceção do Risco em Ensaios Clínicos

Este questionário tem como objetivo **avaliar as práticas de gestão de risco nos centros de investigação em Portugal no que respeita à condução de estudos clínicos com intervenção** (de medicamentos, de dispositivos médicos, técnicas cirúrgicas, etc.).

É convidado(a) a responder a este questionário no âmbito de um projeto de dissertação do Mestrado em Gestão da Investigação Clínica da Universidade Nova de Lisboa - Faculdade de Ciências Médicas.

O objetivo final desta dissertação é desenvolver uma ferramenta que permita às equipas de investigação clínica em Portugal implementar práticas de gestão de risco dos procedimentos de estudos clínicos com intervenção nos seus centros de ensaio.

Os dados obtidos serão tratados e publicados de forma agrupada, ou seja, **não será possível atribuir as respostas obtidas a uma unidade de investigação / instituição específica.**

Irá demorar cerca de **10 minutos** a preencher este questionário. Agradecemos desde já a sua disponibilidade e contribuição.

* Por favor confirme se consente que as suas respostas sejam analisadas no âmbito da dissertação supramencionada.
  - ◯ Consinto
  - ◯ Não Consinto

Identificação do Centro de Ensaio

* Por favor indique em que unidade de investigação / centro de ensaio trabalha?
  (Esta questão servirá apenas para rastrear a obtenção de respostas, não sendo possível atribuir as respostas obtidas a uma unidade de investigação / instituição específica)

* Por favor indique a sua função no centro de investigação / instituição.
  - ◯ Responsável da Unidade de Investigação
  - ◯ Coordenador de estudos / Study Coordinator
  - ◯ Outra

* Indique qual.

* Em quantos estudos clínicos com intervenção, o centro de investigação participou nos últimos 2 anos (inclua apenas estudos iniciados durante este período)?
  - ◯ 1
  - ◯ 2-5
  - ◯ 6-15
  - ◯ 16-30
  - ◯ >30

Considerando os estudos clínicos com intervenção em que o centro de investigação participou nos últimos 5 anos (todos os estudos ativos durante este período mesmo que iniciados previamente), **indique a percentagem aproximada de estudos com intervenção de:**

	Percentagem (%)
Medicamentos	
Dispositivos Médicos	
Outros (com intervenção de regimes alimentares, produtos cosméticos e de higiene corporal, técnica cirúrgica, terapia celular, etc.)	

Práticas de Gestão de Risco

* Quando recebe uma proposta de estudo para avaliação da exequibilidade (feasibility), a Unidade de Investigação ou as equipas de estudo **utilizam, de forma sistemática, alguma ferramenta ou procedimento para identificar e avaliar os riscos associados aos procedimentos no centro de ensaio?** Por favor não considere os eventos adversos.
  - ◯ Sim
  - ◯ Não

* **Indique a(s) razão(ões) pela(s) qual(ais)** a Unidade de Investigação ou as equipas de estudo **utilizam** essa ferramenta ou procedimento? *(selecione as três opções que mais se aplicam)*

  entre 3 e 3 opções
  - ☐ Para cumprir os requisitos ICH-GCP
  - ☐ Para antecipar possíveis dificuldades que o estudo possa apresentar
  - ☐ Para discutir com a direção do centro de estudos a exequibilidade do estudo
  - ☐ Para garantir a segurança dos doentes
  - ☐ Para aumentar a fiabilidade dos dados
  - ☐ Para reduzir os custos
  - ☐ Para determinar o uso de recursos necessários para o estudo
  - ☐ Para negociar os contratos financeiros
  - ☐ Não tenho a certeza
  - ☐ Outra

* Indique qual.

* Descreva sucintamente a ferramenta ou procedimento utilizado.

* **Indique a(s) razão(ões) pela(s) qual(ais)** a Unidade de Investigação ou as equipas de estudo **não utilizam** essa ferramenta ou procedimento? (selecione as três opções que mais se aplicam)

entre 3 e 3 opções

- ☐ Não é um requisito ICH-GCP
- ☐ Não tem(têm) experiência para realizar uma avaliação de risco
- ☐ Demora demasiado tempo
- ☐ É muito caro
- ☐ É demasiado complexo
- ☐ Não tem impacto na segurança dos doentes
- ☐ Não tem utilidade
- ☐ Não tenho a certeza
- ☐ Outro

* Indique qual.

* **Qual(ais) o(s) risco(s) que identifica no seu centro de ensaio** que possam comprometer a aplicação das Boas Práticas Clínicas e o desempenho das equipas de investigação clínica num estudo clínico com intervenção? (selecione todas as que se aplicam)

- ☐ Atrasos na introdução dos dados no CRF (Case Reported Form)
- ☐ Falta de pessoal especializado / profissionalizado / treinado
- ☐ Falta de tempo dos investigadores / equipa de investigação
- ☐ Atrasos na emissão de parecer pela Comissão de Ética local, quando solicitado
- ☐ Demora na negociação e aprovação do contrato financeiro pela Instituição
- ☐ Falta de equipamentos / instalações
- ☐ Instalações para arquivo da documentação de estudo insuficientes
- ☐ Ausência / ineficiência de estrutura de coordenação de estudos
- ☐ Baixa qualidade dos registos clínicos / Inconformidades com os princípios ALCOA (Atribuível, Legível, Contemporâneo, Original, "Accurate"/Preciso)
- ☐ Recrutamento abaixo do esperado
- ☐ Ausência / complexidade de procedimentos operacionais padronizados (Standard Operating Procedures - SOPs)
- ☐ Outro

* Indique qual.

Ferramenta de Gestão de Risco

* Na sua opinião, a Unidade de Investigação ou equipas de estudo utilizariam uma ferramenta de gestão de risco?

(Nota adicional: Uma ferramenta de gestão de risco é usada para identificar os riscos de um estudo clínico e definir estratégias para a prevenção ou mitigação daqueles que comprometam o desempenho da equipa no estudo. Uma ferramenta de gestão de risco pode ser uma SOP, uma *checklist* ou um programa de computador.)

- ○ Sim
- ○ Não
- ○ Talvez

* Justifique a sua resposta.

Quão importantes considera as seguintes caraterísticas / funcionalidades para uma ferramenta de avaliação de risco?

	Pouco Importante	Importante	Muito Importante
* Estar em concordância com as ICH-GCP	○	○	○
* Existir treino para utilização da ferramenta	○	○	○
* Ser intuitiva e de fácil aplicação	○	○	○
* Estar aprovada pelas autoridades regulamentares	○	○	○
* Ter disponível uma versão em papel	○	○	○
* Utilizar um software eletrónico de fácil acesso e uso (MS Word, MS Excel, etc.)	○	○	○
* Ter sido formalmente validada	○	○	○
* Definir claramente os riscos e as medidas a implementar	○	○	○

Indique outras caraterísticas / funcionalidades que considera importantes para uma ferramenta de avaliação de risco?

Appendix B – Ethics Committee's approval

Decisão final sobre o projeto *"Risk Management in Clinical Trials Operations"*

A Comissão de Ética da NMS|FCM-UNL (CEFCM) decidiu, por unanimidade, aprovar, do ponto de vista ético, o projeto de investigação intitulado "*Risk Management in Clinical Trials Operations*" (nº 26/2020/CEFCM), submetido pela Mestranda Ana Margarida Sá Vale, no âmbito da Tese de Mestrado em Gestão da Investigação Clínica.

Lisboa, 23 de abril de 2020

O Presidente da Comissão de Ética,

(Prof. Doutor Diogo Pais)

TO WHOM IT MAY CONCERN

The Ethics Research Committee of NMS|FCM-UNL (CEFCM) has unanimously approved the Project entitled "*Risk Management in Clinical Trials Operations*" (No. 26/2020/CEFCM), submitted by Ana Margarida Sá Vale, student of the Master in Clinical Research Management.

Lisbon, April 23st, 2020

The Chairman of the Ethics Research Committee,

(Diogo Pais, MD, PhD)

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Appendix C – List of participating clinical research sites in the survey

Associação Lusófona para o Desenvolvimento da investigação e Ensino em Ciências da Saúde (ALIES)
Associação para Investigação Biomédica e Inovação em Luz e Imagem (AIBILI)
Associação para Investigação e Desenvolvimento da Faculdade de Medicina da Universidade de Lisboa (AIDFM)
BlueClinical – Unidade de Fase I
Campus Neurológico Sénior (CNS)
Centro Cirúrgico de Coimbra
Centro de Electroencefalografia e Neurofisiologia Clínica (CENC)
Centro de Investigação em Tecnologias e Serviços de Saúde (CINTESIS)
Centro de Medicina de Reabilitação da Região Centro - Rovisco Pais
Centro de Medicina de Reabilitação de Alcoitão
Centro Hospitalar de Entre o Douro e Vouga, E.P.E.
Centro Hospitalar de Lisboa Ocidental, E.P.E.
Centro Hospitalar de Setúbal, E.P.E.
Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E.
Centro Hospitalar do Baixo Vouga, E.P.E.
Centro Hospitalar do Oeste, E.P.E.
Centro Hospitalar e Universitário de Coimbra, E.P.E.
Centro Hospitalar Leiria, E.P.E.
Centro Hospitalar Médio Tejo, EPE
Centro Hospitalar Universitário Cova da Beira, E.P.E.
Centro Hospitalar Universitário de Lisboa Norte, E.P.E. (CIC-CAML)
Centro Hospitalar Universitário de S. João, E.P.E.
Centro Hospitalar Universitário do Algarve, EPE
Centro Hospitalar Universitário do Porto, E.P.E.
Centro Hospitalar Universitário Lisboa Central, E.P.E.
Clínica DaVita Cascais

Clínica DaVita Leiria
Clínica IVI Lisboa
Coimbra Institute for Biomedical Imaging and Translational Research – Instituto de Ciências Nucleares Aplicadas à Saúde (CIBIT–ICNAS)
Comprehensive Health Research Centre (CHRC)
Espaço Médico de Coimbra
Hospitais CUF
Hospitais Lusíadas Saúde
Hospitais Luz Saúde
Hospital da Senhora da Oliveira Guimarães, E.P.E.
Hospital de Braga, E.P.E. (2CA-Braga)
Hospital de Vila Franca de Xira
Hospital Distrital de Santarém, E.P.E.
Hospital Particular do Algarve
Hospital Professor Doutor Fernando Fonseca, E.P.E.
Hospital Santa Maria Maior, E.P.E. – Barcelos
Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E.
NephroCare, Associação Protectora dos Diabéticos de Portugal (APDP)
Unidade Local de Saúde de Castelo Branco, E.P.E.
Unidade Local de Saúde de Matosinhos, E.P.E.
Unidade Local de Saúde do Alto Minho, E.P.E.

Appendix D – Risk Management Tool for Clinical Research Sites' Use

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Data Collection	Safety reporting fails to meet the required timelines				• Site is aware of an SAE/AESI/Special Situation event during holidays/weekends • The agreed method for safety reporting is not available • Site does not have all details of AE • Seriousness information is missing • Investigators delegated to sign the SAE paper reports are not available at the site	• At the SIV, discuss with the sponsor a reporting method that can be accessed remotely and define the accountable person (and back-up) to report the AE. • At the SIV, agreed with the sponsor an alternative method to report AE. • Instruct the team to report AE within the required timelines regardless of the quantity of information available. d. Provide training to investigator regarding classification of any AE in terms of severity, seriousness and causality.		
Data Collection	No restrict access to the Electronic Health Records System by the sponsor's representatives				• EHRS technical limitations	• Study who, among the site's team, have access to EHRS and which content is authorised to edit/consult. • Stablish a standardised procedure to certify copies of the EHRS. • Access if the used EHRS is compliant with ICH-GCP requirements, namely ALCOA principles.		
Data Collection	Delay in data entry/query resolution				• Limited resources to perform data entry • IT connectivity issues at the site • Patient records are not completed with all the data required	• Prioritise the data to be entered in the CRF (safety information or critical visit information first). • Provide checklists to investigators, indicating all the information that should be recorded in the patient's medical records for a given trial.		
Data Collection	Delay in EDC signature by PI				• PI did not complete initial training in the EDC platform • PI access is expired • PI is on holiday and do not have remote access to EDC • PI does not remember the e-mail used to log in to the platform	• When the site is aware that a signature is needed in EDC, FUP with the PI to complete the required training. • When informed that an EDC signature will be required, confirm that PI has the access activated. • At SIV, suggest a back-up investigator for EDC signature.		

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Data Collection	AEs not adequately documented in source documents				• Investigator did not document all AE details in the source documents (severity, seriousness, causality, etc.) • AE reported by a different medical speciality at the site • AE reported by the patient in questionnaires, patient diaries, etc.	• Provide a checklist with the information that should be reported for each AE to the investigators.	[1]	
Data Collection	Missing source documents or lack of document specifying the location of source data				• Lab reports not archived in Patient Files • Reports from external vendors/clinics not available	• Agree with the team and sponsor on the location for every source of data. • Define a responsible person to print and archive source documents (or certified copies) in the Patient File.		
Essential Documents	New safety information not available for all the required study team members				• There is no accountable person for safety review or the accountable person is not available • Safety information is not distributed to all required study members • The agreed method for safety review is not available	• Define an accountable person for safety review and a back-up. • Agreed on the person and method (by e-mail, shared folder, etc.) to distribute the safety information among the team. • Contact sponsor to have access to the safety information by an alternative method.		
Essential Documents	Incomplete/Incorrect site personnel signature log				• Incorrect version of Signature Log used • Study staff delegated by PI but not trained • Tasks incorrectly delegated (tasks not delegated to any member, tasks delegated to the wrong person, etc.)	• When CRA informs the site about a new version of the Signature Log, CRC should collect any previous blank versions kept in the ISF and cross them out with a statement indicating that it is obsolete. Also, all empty rows should be crossed out in the current version in use. • Ensure a new staff member is only delegated after all protocol required training is completed. • Ensure that all tasks are delegated to at least one person and that every person has at least one assigned task.		

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Essential Documents	ISF is not ready for inspection and relevant documents were either not filed, or filed late, or located outside the ISF structure				• Essential documents not received from the sponsor. • Staff signed a document and did not retrieve the original • After obtaining, documentation is sent to the sponsor for archiving but it is not archived in the ISF • Essential documents are common to several studies and it is just archived in one or few studies' ISFs • Essentials documents pending to be signed	• When an essential document is received from the sponsor, it should be printed immediately; alternatively, CRC can create a folder where these documents are downloaded and then periodically printed and archived in the ISF. Ask the sponsor for essential documents that cannot be located. • Confirm the required process regarding internal courier and instruct staff from other departments to send the original documents accordingly. • Finalise documents as they are being completed (for example, crossed out blank fields of Screening Log after the end of recruitment period or training logs once all team is trained in the corresponding document/procedure). • Set up a database for common documents across several studies (CVs, GCPs, Lab ranges and accreditation, calibration certificates, etc.) and archive new versions of those document in the ISF as soon as they are released. • Train staff in the use of electronic signature through the Citizen Card application freely available; ask sponsor if an electronic signature is acceptable. • Review ISF periodically and request the missing documents to the sponsor.		
Essential Documents	Patient File not completed/completed late				• Lab reports not filled or filled late in the Patient File • EHRS is used and certified copies are not printed on time • Incomplete PROs or PROs not archived in the Patient File • Reports of assessments performed outside the site not received or not archived	• At the SIV, agree with the sponsor which documents are expected to be archived in the Patient Files. • Using the schedule of assessments provided in the protocol, define in which source document will each required assessment be recorded throughout the study. Use this document to guide which documents are to be printed and archived in the File (if the sponsor does not have such a document to record source documents location, otherwise use the one made available by sponsor).		

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Essential Documents	Relevant correspondence not archived in ISF regularly				• Site is not sure when to consider an e-mail from the sponsor/vendor as "relevant" for archiving • Relevant correspondence is received very often as the ongoing communication with the sponsor • Relevant communication is done by phone	• Request sponsor to indicate in the body of the e-mail if e-mail is required to be archived in the ISF (according to ICH-GCP (R2), other relevant communications other than regarding site visits are required to be archived such as e-mails containing relevant information/instructions/ guidance) • When a conversation reaches an outcome or conclusion or it is solved, it should be printed immediately; alternatively, CRC can create a folder where these e-mails are downloaded and then periodically printed and archived in the ISF. • When the information transmitted by phone or verbally is relevant, safeguard site by requesting the sponsor to send you a written confirmation by e-mail (examples include any approval/guidance/clarification about the protocol and study procedures - approvals of Medical Monitor regarding a patient to continue in the study or to be excluded, etc.).		
Essential Documents	Delay in contracts signature by PI or Board of Directors				• PI is not available to sign/date on time • Contract takes too long to be sent from the PI's department to the Board of Directors • Board of Directors takes a long to sign the contracts • Board of Directors does not define clinical research as a strategic priority • Board of Directors has limited time	• Ask the sponsor if an electronic signature is acceptable. • Agree with the Board of Directors upon a common and well-established pathway for contracts negotiation and signature for all clinical trials. • Be informed about the upcoming Board's meetings and agreed with them on the timeline to have the contract signed based on these dates. FUP after meetings. • Define with Board and sponsor if an electronic signature is acceptable; provide training in the use of electronic signature through the Citizen Card application freely available. • Agree with the Board of Directors to delegate a member to sign the contracts on behalf of the President/Board of Directors.		

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Essential Documents	Delay in CV collection				• Personnel did not have a recent CV • Personnel is not available to sign and date the CV on time	• Provide the personnel with a simple and short CV template. • Set up a CV database and in case any signature/date is needed, send the last CV for personnel to confirm it is current and signature. • Ask the sponsor if an electronic signature is acceptable.		
Facilities & Supplies	Oversight deficits due to multiple local vendors participating in a trial				• Site is not used to collaborate with the vendors in clinical practice • Vendors are not used to participating in clinical research projects • PI has limited availability to oversight the vendors' activities	• Define a contact person to interact with each contracted vendor on behalf of the PI. • Consider having a person responsible for the collaboration so common issues affecting several trials can be addressed with the vendor by only one person. • At SIV, consider having at least one person by each vendor present so staff can meet each other and agree on each one's responsibilities.		
Facilities & Supplies	Delay in assessments performance (for example, imaging examinations)				• Limited resources at the site • Long waiting lists	• Partner with an external and specialised clinic.		
Facilities & Supplies	Vendors delays in the transfer of data and query resolution				• Vendor is not aware of their responsibilities with the trial and assume the main site will complete the task • Vendor do not follow the agreed communication flow and data is communicated to a different person or not within the required timelines • Inappropriate resource allocation at the vendor for timely query resolution	• Reach the contracted vendor and discuss non-compliance with the signed contract; ask for sponsor help as necessary. • Ensure the vendor is aware of their responsibilities within the study and reinforce the agreed communication pathway defined.		

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Facilities & Supplies	Lack of communication among participating departments at site				• Departments are not being used to collaborate in clinical practice • There is no contact person in the department and information is communicated to several people	• Define the contact person by each Department involved and share this information among all staff. • At SIV, consider having at least one person by department present so staff can meet each other and agree on each one's responsibilities.		
Facilities & Supplies	Miscommunication with central vendors contracted by the sponsor				• Site has no previous experience with the defined central vendor • There is no contact person of the central vendor or site is not aware of the defined contact • Language barrier	• Reach sponsor if it is observed that central vendors are non-compliant with the agreed responsibilities and timelines. • Consider having a template with all central vendors contact person details by study and updated it as long as new contacts details are available. • In communications with vendors, copy the sponsor's representative, usually monitor, so they can facilitate the communication.		
Facilities & Supplies	Change in facilities or equipment suitability				• Equipment broken during the trial • A specific study assessment started to be performed at a different department/room	• Inform the sponsor immediately and discuss the possibility of lending equipment for the time equipment will require to be replaced. • Before the change to the new location, perform feasibility to the new place and inform the sponsor about the new location conditions and expected risks.		
Facilities & Supplies	Study assessments performed by an external vendor				• Site can not ensure study assessments to be performed within the required timelines • Site did not provide the required service	• Consider have a database with relevant information regarding previous collaboration experiences; and consider preferred partners. • Detailed the scope of work and responsibilities through a contract. • Define a person (and a back up) to represent the site in communications; ask the vendor to provide a contact person for administrative and/or technical communication. • Inform sponsor about the agreed communication flow between site-vendor-sponsor.		

CATEGORY	IDENTIFIED RISK	IMPACT	PROBABILITY	TOTAL RISK SCORE	POTENTIAL CAUSES	POTENTIAL CONTROLS / MITIGATION ACTIONS	REFERENCES	RESPONSIBLE
Investigational Product	Investigational product stock is not adequate				• Site not available to receive IP shipment • IP not received at the site in proper conditions (temperature excursion during shipment, compromised /damaged packaging) • IP stock not in proper conditions (expired, damaged, etc.)	• Inform sponsor of the schedule site is available to receive IP (working hours, weekends, planned holidays, etc.). • Inform sponsor immediately of IP not received in proper conditions (update IxRS as applicable) and request additional IP; put the affected IP in quarantine. • Confirm the expiration date of IP before dispensing (for example, adding a column to the accountability log to enter the expiration date for each kit at the time of dispensing).		
Investigational Product	Storage requirements not met for investigational product				• IP not stored at the site as required per protocol/IB (temperature, light and/or humidity requirements) • Storage equipment (fridge, freezer, data loggers, etc.) not available/not working • Storage information not documented appropriately (temperature records unavailable) • Quarantine process not followed to expired/damaged IP • IP handled (received, stored) for non-authorised personnel	• Pharmacy should have facilities that allow for good segregation of IPs and separate from normal pharmacy stock in an area with access restricted to pharmacy staff. • Set up the required equipment at the site initiation and define back-up equipment. • Confirm that temperature reading devices are available, including back-up, and working correctly. • Have a defined label to identify IP in quarantine, clearly segregated from working stock.	[2]	
Investigational Product	Temperature Excursion not noticed/reported				• Pharmacy staff do not have a standardised process to verify the temperature • Datalogger devices are not working properly • Alarm is not working	• Ensure temperature monitoring devices have a valid proof of calibration. • Ensure the existence of back-up devices. • Pharmacy should have written procedures in place for the actions to be taken when the storage conditions are outside of the specified range.	[2]	

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Investigational Product	Wrong kit dispensed to a participant				• IxRS is not updated (received, damaged, quarantined IP nor register) • Kit assignment was not double-checked before the dispensation	• Store the investigational product returned by patients separately. • Update IxRS with the real status of each kit of investigational product. • Define a process to double-check kit assignment against prescription document; consider involving more than one person in the checking process.		
Investigational Product	Multiple studies using the same storage place at the site				• Study-specific kits not clearly identified • Lack of space to have all investigational products separated	• Clearly separate the kits and label the different zones with the study identification		
Staff qualifications & training	PI unavailability				• PI is participating in several studies • PI accumulates other roles within the site	• Have the PI's availability into account during the feasibility and site selection phase and proactively suggest other PI than the one indicated by the sponsor (consider investigators with less clinical research experience and provide the rationale to sponsor). • Consider having a less experienced investigator accompanying the PI-specific activities closely.		
Staff qualifications & training	A study requires clinical trial naïve investigators				• Studies in the therapeutic area are rare at the site • Experienced investigators are responsible for ongoing competitive trials at the site • Turnover of experienced colleagues	• Set up a training session in ICH-GCP and general aspects of clinical research (it can be requested to the sponsor). • Promote meetings between experience and naive investigators to share successful experiences and common barriers across their studies.		
Staff qualifications & training	Staff inadequately trained				• Study personnel not trained on trial-related procedures • Training record is not present • Training record is incomplete	• Ensure a study team member is only delegated after the completion of the required training. • Develop a template to record training provided, including self-training, or request a sponsor's template.		

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Staff qualifications & training	High turnover of study team members				• Natural career progression • Lack of research career recognition	• Inform sponsor as soon as possible about study team members leaving the site both temporarily (for example, due to sick or maternity leave) or permanently (for example, due to retirement or dismissal). • Ensure that, before leaving, the leaving person handover the tasks and required information to the receiving person who will be in charge of those tasks. • As possible, as part of succession planning, ensure the site has at least two people delegated for each task to be performed within the study.		
Study-Specific Procedures	Blinded personnel receive unblinded data				• Staff is not aware of the communication plan to ensure blindness • Staff who performed blinded tasks for a study also perform unblinded tasks for another study	• Review the communication plan with staff at the SIV and regular contacts during the study; ensure unblinded staff is aware of their contact points with sponsor and vendors. • If staff is participating in more than one study requiring blinding procedures, staff should perform blinded/unblinded roles for all studies they are involved in. • Review which documents can unblind the patient treatment (lab results, AE information.		
Study-specific Procedures	Increased complexity due to multiples sub-studies				• Assessments applied to the participants may differ depending on their authorisation to participate or not in a given sub-study • Several ICFs to be signed • Requirement for a greater level of organisation to track subjects participating in each sub-study	• Consider whether multiple informed consent forms need to be administered and provide copies of them along with the main ICF to the investigators who are in charge of presenting the study to participants. • Confirm the additional assessments that need to be performed by participants who accepted to take part in a sub-study; have a clear track of those patients to avoid perform any assessment to participants that do not consent for it.		

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Study-specific Procedures	Network connectivity issues do not allow for ePRO device fully working				• Site's internet does not ensure the full operation of the device • Patient has no enough skill to operate the device	• Confirm if internet connection is adequate for device operation; inform sponsor, ideally during the feasibility phase and, if necessary, request a hotspot to ensure connectivity. • Confirm if alternative methods can be used to complete the PRO (paper, web-based platform, etc.), for example, in case the device is not working correctly.		
Study-specific Procedures	Handling requirements for study samples not met				• Laboratory kit not available or in proper conditions (expired, damaged, etc.) • Samples not collected at the defined timepoint • Samples not processed as required per protocol/laboratory manual • Storage equipment (fridge, freezer, data loggers, etc.) not available/not working • Samples not stored as per requirements (ambient, frozen, etc.) • Courier not contacted / not available • Shipment not done according to the required conditions (ambient, frozen, etc.) • Samples handled (collected, processed, shipped) for non-authorised personnel	• Delegate a site member (and a back-up) to check the laboratory kits stock and its conditions (expiration date, damage, etc.) and define the frequency for this review. • Define the process for the expired or damaged kits to be destroyed or stored away from the usable kits and ensure the study team is aware of the procedure defined. • Delegate a site member (and a back-up) to order laboratory kits in advance. • Provide the person in charge of the samples' collection with pocket guidance for the study assessments. • Train the study team to review the laboratory manual before any sample collection; print the relevant laboratory manual pages for each visit and send it to the person responsible for samples processing and storage. • Delegate a site member (or back-up) to regularly extract temperature records from the fridge/freezer and review them for compliance; Define back-up equipment, and make sure the study team is aware. • Define the process to contact the courier (who contact the courier, where contacts are available, who update contacts if any change occurs, etc.). • Confirm the process to request dry ice boxes for shipment.		

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Study-specific Procedures	Study Visits performed out of the required window per protocol				• Method used to calculate visit windows is incorrect • Visit scheduled based on the visit window for the wrong subject/study • Baseline date for visit window calculation incorrect • Re-schedule a subject's visit without re-confirm visit window • Bank holidays or study personnel/subjects holiday period	• Confirm with the sponsor if there is any available tool to calculate the visit windows. • Avoid the visit window's upper limit to allow visit's re-scheduling if needed (patient or study personnel unavailability, unexpected issue with study equipment, etc.).		
Subject Recruitment and Retention	The study allows the inclusion of vulnerable population (children, inmates, mentally ill)				N/A (not dependent on the site's decision)	• Confirm if there is any specific, informed consent to be signed by these subjects. • Confirm if a legal representative or witness is required during the informed consent process. • Confirm if there are any other considerations for special subject populations (different study assessment; dose modifications; etc.).		
Subject Recruitment and Retention	The study allows the inclusion of women of childbearing potential				N/A (not dependent on the site's decision)	• Confirm the I/E criteria and the protocol requirements for women of childbearing potential. • Discuss with the subject the use of an effective birth control method during the study. • Discuss with the subject the implications of a pregnancy during the study (study drug discontinuation, study withdrawal, etc.). • Confirm if there is any specific, informed consent to be signed in case of pregnancy.		

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Subject Recruitment and Retention	Delay in the patients' reimbursements				• Sponsors reimbursement timelines.	• Require sponsors to define timelines for patient's expenses reimbursement at the financial contract and ensure they are being compliant with those timelines. • Establish a process flow to reimburse patients directly and then having the sponsor reimbursing site.		
Subject Recruitment and Retention	Informed Consent / Reconsent process fails to meet regulatory requirements				• Clinical study procedures conducted before discussing and signing ICF • ICF not signed/dated by the participant (legal representative, witness) or investigator as required • ICF blank fields (investigator contacts, DPO information, etc.) not completed • ICF copy not given to the participant • Use of an outdated version • ICF process not documented in the medical notes • ICF process conducted by non-authorised personnel • ICF amendment not signed in the next patient visit following new ICF implementation • Incomplete ICF signed/dated (for example, not all pages printed due to printer issues)	Define a step-by-step process to present, discuss and sign the ICF at the site. The defined process should be discussed and agreed upon at the SIV. A suggested process flow to avoid common causes is presented below: a. CRC confirms which investigators are trained and delegated to obtain the ICF. b. CRC confirms the applicable version(s) of ICF to be used (confirm whether there are any ICFs other than the main: for genetic purposes, sub-studies, optional procedures, etc.) and provides the investigators with a copy of each document. When a new version is implemented, CRC should collect any previous versions kept by investigators to be destroyed and the copy archived in the ISF should be crossed out with a statement that it is obsolete. c. After the subject's eligibility assessment, the investigator presents the study to the subject and provides the ICF for reading and comprehension. Investigator evaluates if a legal representative/witness is needed. d. CRC further explains to the subject the general aspects of clinical research and the difference from clinical practice and provides a template for the subject to write questions and concerns about the study. e. Subject reads the ICF at the site guided by CRC or at home with family members. f. CRC asks some questions to confirm if the subject understands the study (e.g. what is the purpose of this study?; How long will the study take?; What are the costs of participating in the study?).	[1], [4], [5]	

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						g. Subject discusses the questions and concerns with the investigator. h. Investigator completes the blank fields of ICF and signs the ICF along with the subjects. i. CRC does a quality check of the signed ICF (applicable version(s), all blank fields completed - contacts; signatures and dates, etc.). If ICF is correct, CRC provides a copy of the signed ICF to the patient. If any error is found, ask the investigator / subject to correct it as per ICH-GCP requirements. j. CRC confirms if any study material is to be provided at the ICF signature time (patient cards, diaries, etc.) and explains its usage. k. The investigator / CRC prints the electronic records and confirms if the ICF process is appropriately documented in the patient medical records.		
Subject Recruitment and Retention	Recruitment expectations not met				• I/E criteria are very specific. • Patients diagnosed/treated at a different department not included in the study team. • Recruitment expectation provided is not realistic.	• Confirm if the protocol allows for subject rescreening. • Discuss the patient pathway with the hospital (which medical speciality does the diagnosis; which medical speciality can prescribe the treatment, etc.). • Liaise with patient representatives and colleagues from different hospitals to let them about the study. • In Department meeting, remind that a trial is ongoing and recruiting patients with these eligibility criteria, so the other investigators are aware of them and let them know about the recruitment status.	[6]	
Subject Recruitment and Retention	High number of consent withdrawals				• Study procedures cause an additional burden on the subjects' routine (more frequent visits, more time on site, etc.) • Subjects have to visit several facilities for different procedures (external clinics, different departments within the site, etc.) • Study requires a long period of follow-up	• At the time of consent, review and agree with the subject the assessment flow at each visit and the required time expected. • Ensure proper appointment booking, so the patient has not to be in crowded waiting rooms.	[3]	