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Research Article

An Introduction to Clinical Research

Martina Alberti[1] and Roberto Verna[1-3]*

[1]Research Center for Health and Social System, Guglielmo Marconi University, Roma, Italy

[2]Academy for Health and Clinical Research, Roma, Italy

[3]World Association of Societies of Pathology and Laboratory Medicine - WASPaLM, Italy

***Corresponding Author:** Roberto Verna, Research Center for Health and Social System, Guglielmo Marconi University, Academy for Health and Clinical Research, Roma and World Association of Societies of Pathology and Laboratory Medicine - WASPaLM, Italy.

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Abstract

Clinical trial is any study on humans aimed at discovering or verifying the effects of a new drug or an existing drug being tested for new therapeutic uses, with the aim of determining its safety or efficacy. The trial is divided into several phases and is conducted first in the laboratory and on animal models (preclinical testing) and then on humans (clinical trial).

Keywords: Sponsor; Ethics Committee; Contract Research Organisations (CROs); Good Clinical Practices (GCP); Study Protocol; Principal Investigator (P.I.); Quality

Clinical Research

Clinical Research is a process aimed at verifying and investigating the effects of a new or existing drug tested for a therapeutic use, ascertaining its efficacy and safety profile. Clinical testing is divided into preclinical and clinical. Preclinical testing represents the first phase of testing, conducted through "in vitro" studies on cell cultures and "in vivo" studies on laboratory animals, with the aim of outlining the pharmacokinetic aspects of the molecule, such as the route of administration, therapeutic window and elimination method.

Only after having obtained promising results and having admitted safe therapeutic use criteria, do we move on to "clinical" testing, conducted directly on humans. It is therefore important to underline that clinical testing is a long, expensive and highly risky process that does not always lead to the desired result. It is estimated that, compared to the number of molecules synthesized and studied, many are "killed" during pre-clinical studies and only a few manage to achieve marketing authorization (AIC) with a specific therapeutic indication.

Clinical studies can be classified into four phases, which intersect with each other based on updates on the knowledge of the intrinsic characteristics of the experimental drug and on the data obtained during the trial.

- **Phase I:** Aims to provide the first results in terms of efficacy and tolerability of the drug, defining the maximum effective dose and the pharmacokinetic parameters of absorption, distribution, metabolism and excretion, as well as the preferred route of administration. If the drug demonstrates an acceptable level of toxicity compared to the expected benefit, it can move on to the next phase of the trial.
- **Phase II:** Is aimed at evaluating the therapeutic activity of the new drug. The best dose to administer is also determined. The evaluations of the activity and safety parameters can be "single-blind" or "double-blind", therefore without the patient or the doctor and the patient knowing the type of treatment received or administered.

- **Phase III:** It has the objective of demonstrating the efficacy of the drug and evaluating its benefit/risk ratio on the greatest possible number of people, carriers of the disease for which the drug is being studied. Once Phase III is completed, it is possible to request marketing authorization (AIC) from the regulatory bodies.
- **Phase IV:** Also called post-authorization or post-marketing surveillance study. In this phase, further and new information is acquired and the rarest adverse reactions that may become detectable with large-scale use of the drug are evaluated [1].

Endpoints and sample size in clinical trials

Endpoints are defined as results, specific measures or events used to evaluate the effect of a treatment. The primary endpoints, the most important outcomes of a study, represent the reference parameter for defining the success or failure of the trial. Secondary endpoints are instead used to collect more complete and in-depth data, valuable information on other aspects of the treatment – positive or negative – that would otherwise not be visible. Sample size refers to the number of individuals required to effectively conduct a study.

Clinical trial subjects

In order for the clinical trial to be conducted correctly and in compliance with Good Clinical Practices (GCP), it is necessary for different entities that take part in it at multiple levels to collaborate, cooperate and share responsibilities.

The Sponsor: who under his own responsibility initiates, manages and/or finances a clinical trial (1.53 GCP).

Contract Research Organisations (CROs) [2]: Independent companies hired by the sponsor to manage the activities related to the promoted trial. The sponsor remains primarily responsible for the integrity of the data and the high quality standards required for the conduct of the clinical trial. The nature of the minimum requirements and many of the activities of the CROs are regulated by the Ministerial Decree of 15 November 2011 "Definition of the minimum requirements for contract research organizations (CROs) in the context of clinical trials of medicinal products" and described in section 5.2 of the Good Clinical Practice (GCP). The tasks of the CROs are the drafting of the clinical protocol, the submission of documents to regulatory bodies and ethics committees, data management, the preparation of the Product Monograph, the design and proposal of the CRF (Case Report Form). The activity most delegated by Sponsors to CROs is clinical monitoring, assigned to professional figures called Clinical Research Associates (CRAs) or "monitors". The monitoring activity can be performed remotely and on-site and includes:

- **Pre-study Visit (PSV):** Qualification visit of the experimental center;
- **Site Initiation Visit (SIV):** Start of study visit;
- **Monitoring Visit (MV):** Monitoring visits once the study has started;
- **Close-Out Visit (COV):** End of study visit.

The investigator (or Principal Investigator - PI): Is the medical doctor who is entrusted with the conduct of the clinical trial within an experimental center and whose training must be proven by an adequate CV. He or she is required to scrupulously follow the study protocol, without making any changes or deviations, unless "there is an immediate danger to the subjects participating in the trial without prior approval/favorable opinion of the ethics committee" (GCP 4.5.4). Therefore, he/she must know the technical characteristics that are listed and described in the Investigator's Brochure (IB) and the methods of storing the drug. A fundamental role of the PI is to obtain Informed Consent from the subject candidate for the study and to report to the sponsor all serious adverse events (SAE) within the timeframes and methods set out in the protocol. Reports of serious and unexpected adverse drug reactions (SUSAR) must also be reported to the regulatory authorities and the ethics committee.

The Ethics Committee (EC): Is an independent regional, national or supranational structure, composed of professionals with the role of providing a favorable ethical and feasibility opinion regarding the study protocol. The ethical, scientific and methodological evaluation of clinical studies by the ethics committee has as its reference what is set out in Legislative Decree no. 211 of 2003, the Helsinki Declaration in its most updated version, the Oviedo Convention, the

aforementioned rules of good clinical practice (section 3 of Good Clinical Practice) regarding the submission by the Sponsor or delegated CRO of the study protocol together with other extremely important documents such as the Informed Consent (ICF), the Investigator's Dossier (IB), the Experimental Drug Dossier and related monograph and the contract signed by the Sponsor and the Experimental Center [3].

Guideline on regulatory simplification and elements of decentralization for the purposes of conducting clinical trials of medicinal products

Determination 424 – 2024 [4] constitutes a Guideline applicable to clinical trials on materials and is aimed at specific organizational aspects regarding the submission of application documentation and conditions of clinical trials. Taking into account the principles established by Regulation (EU) no. 536/2014 [5] relating to the submission of the application for authorization to clinical trials, this guideline provides clarifications so that provisions contained or not prohibited in European standards and guidelines can be correctly applied at national level. The topics examined concern.

Use of third-party service providers

Sometimes, the complexity of clinical trials may require the activation of third-party service providers to perform tasks that the experimental site is unable to provide and support. In accordance with ICH – GCP, the promoter of the trial is assigned the responsibility of deciding the experimental design and the organization of its execution, including the ability to involve, in advance or at the request of the experimental site, third-party service providers. Although not in conflict with current legislation, some aspects are recommended such as:

- The distinction of the roles and responsibilities of the promoter and the experimental site regarding the management of the service provider involved, the tasks required of it and the protection of data, avoiding situations of conflict of interest.
- Adequate training on the study protocol and the tasks to be performed by the third-party service provider and maintaining responsibility for all medical decisions regarding the conduct of the trial by the principal investigator.
- The stipulation of a specific contract between the service provider and the sponsor in which the assigned tasks are outlined and the responsibilities established for the processing of personal data are established.

Expense reimbursement for participants in clinical trials

Participants in clinical trials are granted reimbursement for expenses incurred in traveling to the experimental center provided that the methods and criteria for reimbursement are previously included in the Initial Application dossier and submitted to the Ethics Committee for evaluation in the documentation relating to Part II of the experimental dossier.

Loss of earnings compensation for participants in clinical trials

It is permitted to provide for a loss of earnings compensation only in the case of healthy volunteers, whose application criteria are similar to expense reimbursement.

Delivery of the experimental drug to the participants' homes

Regulation (EU) No. 536/2014 requires complete traceability of the experimental drug, but does not place limitations on delivery to participants. Although the experimental drug is usually delivered by the promoter to the pharmacy of the experimental site that takes care of the control, registration and storage, it is possible to provide for direct delivery to the participant's home via the hospital pharmacy through an appropriate risk assessment when the conditions, methods of transport and storage allow it.

Allocation of costs related to experimental and auxiliary drugs

In Italy, the cost of no experimental or auxiliary drug, medical device or procedures foreseen by the experimental protocol must be charged to the participant, to the SSN or to the experimental site, in compliance with the principle according to which no additional expense must be charged to the participants in the trial or to public finances. In this regard, the promoter is responsible for the costs associated with the distribution of all experimental drugs, medical devices or procedures foreseen by the protocol, including drugs with AIC in Italy used according to and outside the authorization conditions and the substances used to produce physiological reactions necessary for the implementation of the trial (Challenge Agents).

However, it should be emphasized that the subject or the NHS, depending on the conditions, are responsible for the drugs used for background therapies and the drugs not subject to the trial that would have been administered to the subjects regardless of their participation in the clinical trial.

Clinical trials in extra-hospital settings

It is permitted to use clinical centers outside of hospital facilities in the context of carrying out clinical trials relating to public health conditions.

The concept of quality and the quality management system

The quality of a product, service or performance means the concept of "meeting the specifications", i.e. the set of all the characteristics that converge to satisfy the needs of the customer and the user. These characteristics cannot ignore the activities coordinated by different functions that collaborate to make this happen.

In this context, the Quality Management System (QMS) constitutes the macrostructure of the connected and interdependent activities that influence the final quality of a product or service provided. The UNI EN ISO 9001:2015 Standard defines the adoption of a Quality Management System, for an organization, as "a strategic decision that allows to improve the overall performance and to build a solid foundation for development initiatives". Furthermore, the UNI EN ISO 9001:2015 Standard defines the principles and concepts of the Quality Management System and is aimed at supporting users by providing indications applicable to varied business situations in terms of both size and complexity, in order to be able to design and implement one that is adaptable to their condition. Generally speaking, in order to achieve this objective, it is necessary to identify the outputs and manage processes and resources so as to be able to achieve the desired results [6].

Management of processes and the system as a whole can be achieved using the Plan-Do-Check-Act (PDCA) cycle, which involves the systematic definition and monitoring of the processes and their interactions, in order to achieve the expected results in accordance with the company's policy and strategic directions.

- **Plan:** Establish the objectives of the system and its processes and the resources necessary to provide results in accordance with the customer's requirements and the organization's policy, and identify risks and development opportunities.
- **Do:** Carry out what was previously planned.
- **Check:** Check and measure, when possible, the results obtained against the objectives to be achieved and the pre-established endpoints.
- **Act:** Develop processes to correct and mitigate any deviations or improve performance.

Figure 1: PDCA Cycle: Plan – Do – Check – Act.

Efficient Quality Management Systems are based on organized and updated documentation that, in principle, includes:

- **Quality Manual:** Constitutes the company's "identity card" and is drawn up internally, describes the company policy and philosophy, provides an overview of the objectives that must be achieved and the standards used for the development and processing of each process.
- **Standard Operating Procedures (SOP):** Are an essential tool for the application of quality criteria, as they report detailed instructions on how a specific process must be carried out, as well as the functions responsible for applying what is described.

- **Data management system:** Essential for providing objective evidence of the activities carried out according to company standards, in compliance with ALCOA+ principles and data integrity requirements.

The quality management system in clinical trials

In the context of clinical trials, the Quality Management System consists of three macro-areas that allow the achievement of the desired satisfaction criteria:

- **Planning of quality standards:** At the basis of the management system, it is necessary to define the standards and methods to achieve the expected satisfaction and success criteria.
- **Quality Assurance:** This involves the implementation of all strategic control activities planned to be able to satisfy the planned requirements.
- **Quality control:** It is the actual monitoring of the processing methods of a process and of specific results compared to a target useful for determining whether the workflow is conducted in accordance with the planned standards and to implement the methodologies defined for the elimination or mitigation of the causes that lead to unwanted goals.

Although all the figures who collaborate and cooperate in the success of the experimental project are substantially involved in quality assurance in all phases, the main functions that hold the responsibility for quality assurance and control are the following:

- **CRA:** Ensures that all the personnel involved in a clinical study at an experimental center know in detail all the procedures envisaged by the study protocol and the quality standards to be respected, as well as that all the participants in the study are made aware of the objectives and practices being studied, through specific information and/or informed consent.
- **QA Auditor:** These are highly specialized figures whose role lies in verifying the relevance to the company procedures, policies and work instructions. Audits, conducted at the Sponsors and CROs, can be internal, if they are carried out by internal auditors established by the company QMS, or external, if they are carried out by the Regulatory Authorities. In this regard, the sponsor is required to notify the Principal Investigator of the upcoming inspection so that he can prepare all the documentation in original format relating to the ongoing trial.
- **Ethics Committee:** Made up of figures specialized in the scientific and non-scientific field, it is responsible for judging and expressing an opinion on the feasibility of the study after having carefully examined the protocol and the attached documentation. During the trial, it ensures that all processes are carried out in accordance with the qualitative guidelines and the sponsor's criteria and intervenes promptly in the event of deviations.

Risk-based thinking

A structured Quality Management System implies the risk-based thinking approach that allows the company organization to determine in advance what the "risk factors" could be that could trigger a deviation from the processes and, therefore, from the planned results. In this regard, it is a method that allows the application of preventive actions and non-conformity analysis to minimize negative effects, taking into account the final objectives set.

The UNI EN ISO 9001:2015 standard defines risk-based thinking as an essential requirement for an effective Quality Management system and, within a business context, it is essential to plan and execute actions to address new opportunities and associated risks, with the aim of pursuing better results by preventing the negative effects caused by deviations.

Risk arises from uncertainty about actions and processes, any uncertainty can have negative and positive implications. A positive deviation resulting from a risk can translate into opportunities. Opportunities can emerge as the result of a favorable situation that, in certain circumstances, allows the organization to attract customers, develop new services and products, reduce waste and improve productivity.

Risk-based quality management in clinical trials

"Risk-based quality management" is the concatenation of structured processes that allows the evaluation, control, communication and review of risks associated with the planning and conduct of

clinical trials and the development of experimental programs. The application of these processes underpins the Quality Management System which, in most cases, consists of documents such as Standard Operating Procedures (SOP), company policy, work instructions, forms and templates [7].

As documented in section 5.1 of Good Clinical Practices, it is the responsibility of the Sponsor of the trial to use highly specialized systems that guarantee quality control and assurance, as well as qualified personnel to supervise and carry out the trial, manage and verify data, perform statistical analyses and prepare trial reports. Furthermore, all tasks delegated by the Sponsor to a CRO must be documented in writing so that it can take charge and assume responsibility for them [8].

More specifically, according to ICH E6 (R2), the Sponsor must ensure a quality management system during all phases of the trial to ensure the protection of the participating subjects and the reliability and truthfulness of the results obtained. Therefore, Quality Management must lay the foundations of an efficient study design, including tools and procedures for data collection and processing in proportion to the assessment of the associated risks.

The identification by the sponsor of the risks associated with the study, both of a systematic-organizational and clinical nature, allows for the evaluation of the possibility of error and deviation from the process, establishing their impact on the enrolled subject and on the quality of the data produced. Similarly, defining which risks are acceptable and which are critical allows for the implementation of reduction actions, creating activity monitoring plans and training and follow-up sessions on procedures and processes. The a priori definition of the quality standards to be pursued allows for the limitation of deviations from the protocol and for the application of corrective actions more quickly and efficiently. In fact, the Sponsor is responsible for documenting all activities related to risk-based quality management and reporting all deviations from the tolerance margins found, so as to facilitate the risk review process during the conduct of the trial.

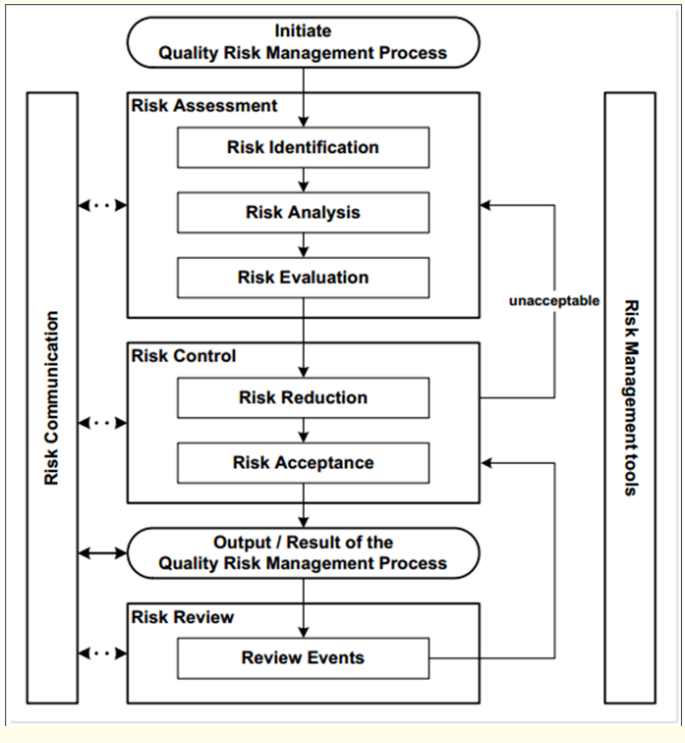

Figure 2: A typical Risk – based Quality Management system.

As outlined in figure 2, risk-based Quality Management includes three macro-areas.

Risk Identification - By convention, risks are classified into general risks, which can cause damage to the clinical study development process indirectly, and therefore related to the organization of responsibilities, functions and structures or associated with the regulatory and ethical context, and risks directly related to the trial being analyzed. Direct risks, on the other hand, are, in turn, divided into risk areas:

- **Area related to the experimental medicinal product or Investigational Medicinal Product (IMP):** In this regard, an accurate evaluation of the available information regarding the chemical-physical, pharmacokinetic and toxicological properties of the active compound is mandatory, as well as the manufacturing, primary and secondary packaging and labeling requirements.
- **Area related to the study design:** The complexity of the study protocol, the vulnerability and morbidity of the participants, as well as the size of the sample to be used and the eligibility criteria are taken into consideration.
- **Area related to operational risks:** Includes the study budget, deadlines and milestones, the preparation of medical and non-medical staff, the selection of hospital centers and their management, the selection of CROs and third-party service providers, monitoring activities and management of data collected through appropriate computerized systems and the timeliness in reporting adverse reactions.

Risk Evaluation – After identifying the risks, it is necessary to understand which processes deserve priority for action, i.e. identify the set of strategic factors that allow obtaining a promising result from a clinical point of view in compliance with GCP and current regulations and the target requirements set by the Sponsor. This prioritization must be justified by the choice of appropriate study documentation, human resources and systematic control and monitoring procedures. Furthermore, risk assessment must be an ongoing process that proceeds in step with the progress of the clinical trial, aimed at optimizing and implementing action strategies based on the needs and data produced.

Risk control, mitigation and acceptance – It is identified as the set of processes that aim to undertake actions aimed at reducing the assessed risk. The application of the risk mitigation plan must have the aim of reducing the risks to a level of acceptability defined a priori. Therefore, efforts in terms of human and economic resources for a systematic control of the risk should be at least proportional to the significance of the risk. In other words, it is essential to implement a fair compromise between risks, benefits, resources employed and budget used. Only risks that do not significantly impact the well-being and safety of the subjects enrolled and the integrity of the data produced can be accepted without any precautionary measures taken, all the others must be complied with within the risk management plan [9].

Risk review and reporting – Although the strategic approach of performing an initial impact assessment allows for the implementation of an appropriate mitigation plan, the possibility that, during the experimentation, new risks may arise based on the progress and data produced cannot be totally excluded. In this respect, review and reporting actions require the production of data and outputs compared to those desired and/or planned. Similarly, appropriate documentation of each deviation from the protocol and each corrective action implemented through an ad hoc CAPA plan, including measurements taken and timing adopted, allows for the analysis of compliance by the experimental centers with the outlined processes.

If, on the one hand, the application of the risk-based quality management plan has as its objective the protection of the human rights of the subjects enrolled, their safety and integrity and the assurance of the quality of the results obtained from the experimentation, on the other hand, the application of a "standardized" planned system does not generate the same degree of effectiveness in all clinical trials. In fact, the extreme complexity of the experimental protocols, the type of study, be it observational, interventional or post-registration, does not allow the application of a single methodology. In this regard, in recent times, a stratified approach to risk categorization has proven useful, taking into account not only the characteristics of the experimental drug, but also the study protocol and its laboriousness, the sample size, the administration route used and therapeutic indications.

Risk analysis in clinical trials: Theoretical outline and practical application

As described above, risks and their potential harmful effects in clinical trials can be directly or indirectly related to the scope of application and, consequently, an effective assessment aligned with Good Clinical Practice and current regulations must take into account several factors that could have a significant impact on the progress and results obtained.

In general, in the initial phase of the risk analysis, the intended use of the experimental medicinal product and the objectives of the study must be specified with extreme clarity. Furthermore, "off-label" use must be taken into account, i.e. "outside the intended use" attributed with the AIC, which could generate additional risks. Therefore, there will be dangers deriving from the correct and intended use of the product and dangers deriving from "off-label" use that must be included in the Summary of Product Characteristics (SPC). Secondly, it is necessary to examine the monitoring method that one wishes to pursue, the possible supply of the drug from third countries, the delegation of some functions to third-party service providers, the quality of the systems used for data production. For example, in the case of an experimental drug, one of the possible dangers could be bacterial contamination, to which is added the complexity of the legislation and documentation to be produced by the importing company if the drug is imported from third countries.

An effective way to conduct the risk analysis is to identify each step necessary to obtain the desired final result, that is, to associate specific dangers with each step that could cause damage to both the end user and the organizational apparatus (Sponsor, Pharmaceutical Industry, hospital, CRO). Basically, a dangerous situation is identified as the circumstance in which people and the environment are exposed to one or more sources of damage: the selective identification of each of them and the application of precautionary measures aimed at minimizing their consequences allows for more effective and impactful control and prevention. On the other hand, to perform an appropriate risk assessment, it is essential to ensure the robustness of the starting data, since they determine the quality of the output.

Attributing the effect of the damage on the patient, on the quality of the product or for regulatory compliance is possible by applying a qualitative or quantitative estimate of the risk associated with the identified danger. Therefore, it is necessary to assign a score depending on the severity and probability of manifestation of the risk.

- The severity provides an assessment of the consequences of a clinical event or damage on the patient/organization. Depending on the degree, the risk can be Critical, severe, serious, minor or negligible in decreasing order.
- The probability of manifestation of the risk is a measure of the probability that this will occur. Depending on the degree, the risk can be Frequent, probable, occasional, rare, unlikely in decreasing order.

By combining the different possibilities, a risk acceptability matrix or "risk heat map" is obtained based on which to establish whether it is necessary to undertake mitigation actions [10].

NOTE: (This figure has been reproposed in Black and White in case of impossibility to print it in colors).

The possible options, based on the results obtained, include:

- Mandatory implementation of precautionary and mitigation measures only for critical and high-level risks and evaluation of the best strategy to use for low and moderate-level risks depending on the case.
- Employ risk reduction methodologies with the broadest possible spectrum, i.e. contemplate strategies applicable to all types of risk, regardless of the severity or probability of occurrence.

With regard to the preparation of the trial and the supply of the drug being tested, as well as the distribution to the subjects enrolled in accordance with the characteristics of the product, it is

Impact	Likelihood				
	Rare	Unlikely	Possible	Likely	Almost certain
Catastrophic	moderate	moderate	high	critical	critical
Major	low	moderate	moderate	high	critical
Moderate	low	moderate	moderate	moderate	high
Minor	very low	low	moderate	moderate	moderate
Insignificant	very low	very low	low	low	moderate

Figure 3: Risk acceptability matrix by severity and probability of occurrence.

important to evaluate what the general provisions are for the possible importation of the drug, the non-adherence of which could have significant implications on the progress of the study.

Directive 2001/20/EC concerning the legislative, regulatory and administrative provisions relating to the application of GCP in the conduct of clinical trials of medicinal products establishes the obligation, on the part of all manufacturers of medicinal products being tested, to request the authorization for manufacturing and importation or Manufacturing and Importation Authorization (MIA) to be submitted to the competent authorities to request the Clinical Trial Authorization. Each MIA holder must make available a QP for the QP Declaration, to be reported in a special register available to the competent authorities for a period of not less than five years [8].

For clinical trials conducted in the EU that require the importation of the investigational drug from third countries, the Sponsor or the delegated CRO must conduct a thorough risk analysis during all phases of the clinical trial, starting from the initial feasibility and budget analysis up to the end of the trial, including the steps in which the study is fully underway. The associated risks could be non-compliance with European GMP during the manufacturing process of the investigational drug or the absence, at the production site, of a qualified QP, as specified in the directive. Although the latter are unlikely but severe, and therefore of a "low" grade, the resulting impact is a delay in the start of the trial and in patient enrollment, caused by a latency in the production and approval by the competent authorities of the necessary documentation. Furthermore, one should not underestimate the risks associated with the procurement and delivery of the experimental drug to the patient, which should normally take place under highly controlled conditions to guarantee the initial properties documented in the SmPC, whose delay in transport and supply in adequate quantities would cause an extreme slowness in the continuation of the study and a huge gap for the processing of the data in progress.

Conclusion

Ultimately, an adequate risk analysis in the initial phases of the study design always leads to the categorization of risky events on the basis of a risk acceptability matrix, to allow, in the subsequent stages, the application of the concepts related to the CAPA Plan, which aim to reduce and mitigate the probability that these events will occur.

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