Essays

Ethical, Deontological and Regulatory Challenges in Contemporary Clinical Trials: Implications for Scientific Research Institutions in the EU

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ABSTRACT: Clinical trials are fundamental to biomedical research, enabling the systematic evaluation of new drugs, devices, and interventions for safety and efficacy. Conducted in progressive phases, they follow rigorous ethical, scientific, and regulatory standards to ensure participant protection and data reliability. Despite their pivotal role in medical innovation, trials are resource-intensive and financially demanding. Ethical frameworks such as the Declaration of Helsinki and Good Clinical Practice guide their conduct, while post-marketing surveillance ensures ongoing safety monitoring. The role of clinical trials, together with their ethical and institutional aspects, is examined with particular attention to current challenges and regulatory developments.

KEYWORDS: Clinical trials; drug development; regulatory compliance; good clinical practice; ethics; deontology

SUMMARY: 1. Clinical Trials: Definition and Characteristics – 2. The Importance of Clinical Trials in Drug Development – 3. Ethical and Deontological Aspects of Clinical Trials – 4. Economic Aspects of Clinical Trials – 5. Post-Marketing Evaluation Methods – 6. Scientific Institutions and Their Role in Clinical Trials – 7. Conclusion.

1. Clinical Trials: Definition and Characteristics

Clinical trials are a type of research designed to investigates novel treatments and tests, assessing their impact on human health outcomes.[1] According to the definition provided by the National Institutes of Health (NIH), a study can be classified as a clinical trial if it meets the following four criteria:

- The study involves human participants,
- The participants are prospectively assigned to an intervention,
- The study is designed to evaluate the effect of the intervention on the participants,
- The effect is being evaluated on a health-related biomedical or behavioural outcome.

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[1] https://www.who.int/health-topics/clinical-trials/#tab=tab_1 (last visited 15/10/2025).

Importantly, the NIH definition of a clinical trial still applies even if the study includes healthy participants, lacks a comparison group (e.g., placebo or active control), is focused solely on assessing pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug, involves a behavioural intervention, or measures intent to change behaviour, as long as at least one aim or sub-aim of the study qualifies as a clinical trial.[2]

Clinical trials are conducted after preclinical investigations, which include animal studies and assessments of drug production and purity. These preclinical phases focus on evaluating the drug's safety in doses approximating human exposures, as well as its pharmacodynamics and pharmacokinetics. After these stages, clinical trials are carried out in four phases, each with a distinct purpose. Researchers actively recruit new participants for each phase.

Phase I trials (also referred as "dose escalation" or "human pharmacology" studies) are the first trials testing the experimental drug in humans, typically in a small group of healthy or diseased volunteers. The aim of Phase I is to assess the safety and determined the maximum tolerated dose of the drug, but also its pharmacokinetics.

Phase II trials (also referred as "therapeutic exploratory" trials) are performed in a small group of participants who have the disease of interest. This phase is designed to test safety, pharmacokinetics and pharmacodynamics, and may also gather data to inform the design of Phase III trials (such as determining optimal doses, dosing frequencies, administration routes, and endpoints). Phase II trials may also offer preliminary evidence of drug efficacy; however, the small number of participants limit supports the necessity of a subsequent Phase III trials.

Based on prior studies, Phase III trial (also referred as "therapeutic confirmatory", "comparative efficacy", or "pivotal trial") involve a larger and often more diverse population. Their main aim is to confirm or refute the drug's efficacy and identify common adverse reactions. Phase III trials are most commonly "superiority" trials, where the experimental drug is compared to a standard therapy or a placebo. Another type of Phase III trial is the "equivalence" or "positive-control" trial, designed to verify if the experimental treatment is similar to the chosen comparator. A variation of the equivalence trial is the "non-inferiority" study, which seeks to prove that the experimental treatment is not less effective than the standard by a pre-specified margin.

A hallmark of Phase III trials is treatment allocation balance, achieved through randomization. This method helps to eliminate confounders and any biases between treatment groups. Additionally, Phase III trials are often "blinded" (or masked) to minimize assessment bias. Blinding strategies can include single blinding (subject only), double blinding (both subject and investigator), or triple blinding (data analyst, subject, and investigator).

All clinical trials for marketing authorization of human medicines in the European Union must comply with EU clinical trial regulations, while trials conducted outside the EU must adhere to ethical standards equivalent to those in the European Economic Area, including international good clinical practice and the Declaration of Helsinki.[3]

[2] https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/definition (last visited 15/10/2025).

[3] J.I. HALONEN, M. ERHOLA, E. FURMAN, *et al., The Helsinki Declaration 2020: Europe that protects*, 4, 11, 2020, e503-e505.

Once a drug is approved, regulatory agencies may require Phase IV (post-marketing) studies. These observational studies evaluate the long-term effects of the drug, including less common adverse reactions, and assess its cost-effectiveness or effectiveness in populations or conditions different from those in the original trials. Post-marketing studies are essential because pre-marketing (Phase III) trials often do not capture rare side effects or long-term outcomes. Approximately 20% of drugs receive new black box warnings after marketing approval, and most post-marketing drug withdrawals are due to previously unanticipated adverse reactions.

The structured progression of clinical trial phases ensures methodological rigor but also reveals increasing complexity: each phase adds ethical, logistical, and financial burdens. This tension between scientific robustness and operational feasibility highlights the need for updated governance models capable of integrating ethical, regulatory, and technological dimensions.

This sets the stage for understanding why clinical trials are not only scientific tools but also ethical and institutional challenges.

2. The Importance of Clinical Trials in Drug Development

Clinical trials constitute a cornerstone for advancing biomedical knowledge and improving clinical outcomes in patients. They provide robust evidence on disease pathophysiology, treatment efficacy and safety, and interindividual variability in therapeutic response. These studies deepen scientific understanding, inform future research directions, and support regulatory decision-making processes. The evidence generated serves as the foundation for marketing authorization of medicinal products and fosters the development of innovative therapeutic interventions for the benefit of public health and patients worldwide. However, approximately 90% of clinical trials fail to obtain regulatory approval.[4] Beyond the substantial economic losses associated with unsuccessful studies, such failures delay patient access to potentially life-saving therapies and raise important ethical concerns, as participants may be exposed to risks without deriving direct therapeutic benefits.[5]

Clinical trials constitute an indispensable scientific mechanism but also expose profound challenges: high failure rates, escalating costs, and ethical tensions related to risk–benefit balance. These issues demonstrate the need for not only methodological improvement but also institutional strategies that reconcile innovation with ethical responsibility. This leads naturally to the ethical-deontological questions examined in the next section.

3. Ethical and Deontological Aspects of Clinical Trials

Although the ethical conduct of medicine had been a central concern since antiquity, it was only in 1947 that ethical principles to guide medical research were first codified.[6] The Nuremberg Code, born from the homonymous International Military Tribunal, established ethical principles for biomedical experi-

[4] D. Sun, W. Gao, H. Hu, S. Zhou, *Why 90% of clinical drug development fails and how to improve it?*, in *Acta pharmaceutica Sinica B*, 12, 7, 2022, 3049-3062.

[5] D.A. Zarin, S.N. Goodman, J. Kimmelman, *Harms From Uninformative Clinical Trials, in Journal of the American Medical Association*, 322, 9, 2019, 813–814.

[6] E. Shuster, *Fifty years later: the significance of the Nuremberg Code,* 337, 20, 1997, 1436–1440.

mentation. This Code was further developed by the World Medical Association's Declaration of Helsinki in 1964.[7] In 1996, the International Conference on Harmonization of Good Clinical Practice (GCP) achieved an international standard for the design, conduct, recording and reporting of clinical trials involving humans. GCP was later endorsed by the EU Clinical Trials Directive 2001/20/EC, which has been replaced by the EU Clinical Trials Regulations 536/2014 (CTR 2014).[8]

Specifically, prior to the trial, the foreseeable risks and inconveniences must be weighed against the potential benefits for the individual subjects and future patients, ensuring that the risks are justified. The safety, rights, and well-being of participants must be the primary consideration, taking precedence over scientific and societal interests. Sufficient non-clinical and clinical data must be available to support the trial, which should follow a clear, detailed protocol approved by an ethics committee. Medical care and decisions regarding the trial subjects are the responsibility of qualified healthcare professionals, and all individuals involved in the trial must have the appropriate qualifications and experience for their assigned tasks.

Freely given informed consent must be obtained from all participants before enrolling in the trial, and all clinical trial data must be recorded, managed, and stored in a way that ensures subject confidentiality in compliance with data protection laws. Investigational medicinal products used in the trial must be manufactured, imported, handled, and stored according to the Good Manufacturing Practice (GMP) guidelines and used according to the approved protocol. Systems and procedures must be in place to assure the quality of all aspects of the trial.

In the context of clinical trials, the Code of Ethics represents an additional layer of assurance, ensuring that researchers and healthcare professionals involved are committed to protecting the rights and well-being of participants. It defines a set of ethical and behavioral principles that guide the conduct of healthcare professionals, emphasizing the importance of personal and collective responsibility in carrying out clinical research. Key principles include respect for human dignity, which requires treating every participant fairly and without discrimination, and the duty to act always in the patient's best interest, avoiding conflicts of interest that could compromise the integrity of the study. Furthermore, the Code of Ethics highlights the need to maintain professional competence through continuous education and specific training on trial protocols, in order to guarantee high standards of quality and safety. Another fundamental aspect concerns the protection of privacy and confidentiality, which implies careful management of personal and sensitive data collected during the trial, in compliance with current data protection regulations. Finally, the Code of Ethics serves as a guide in managing the difficult ethical situations that may arise during research, promoting an attitude of transparency, honesty, and responsibility towards participants and the scientific community.

Recent research is bringing to light a series of new ethical challenges that traditional frameworks were not fully designed to address. For instance, decentralized clinical trials (DCTs) redistribute responsibilities across clinical sites and digital platforms, making it less clear who is accountable for ensuring participant safety and data integrity. Moreover, the use of artificial intelligence in patient recruitment and automated monitoring adds further complexity. It raises concerns about the transparency of algorithmic

[7] World Medical Association, *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects*, 310, 20, 2013, 2191–2194.

[8] https://eur-lex.europa.eu/eli/reg/2014/536/oj/eng (last visited 15/10/2025).

decisions and the possibility of bias influencing who gets selected for a study or how their data is interpreted. At the same time, continuous data collection through wearable devices pushes the boundaries of conventional informed consent. Participation is no longer confined to specific research encounters but involves an ongoing flow of potentially sensitive information. Finally, the integration of real-world data complicates efforts to protect privacy and forces researchers to confront difficult questions about long-term data governance, including how information should be stored, who can access it, and for what purposes.

Foundational ethical principles remain essential, yet they require reinterpretation in the context of digitalization and decentralization. The evolving ecosystem demands dynamic ethical governance that goes beyond static regulatory frameworks and actively addresses new technological risks. These ethical tensions intersect with the equally challenging economic landscape of modern clinical trials.

4. Economic Aspects of Clinical Trials

Clinical trials represent one of the most expensive aspects of drug development. Trial costs vary widely across phases, ranging from approximately $1-4 million for Phase I studies to over $100 million for Phase III.[9] High costs stem from several core components: study design and regulatory submissions, patient recruitment and retention, site operations, laboratory and imaging assessments, investigational product manufacturing, and data management systems that ensure compliance with Good Clinical Practice (GCP) and international standards. Moreover, qualified personnel, such as investigators, coordinators, statisticians, and regulatory experts, represent a significant share of total expenditures. Regional differences are also substantial. The United States remains the most expensive location for clinical research due to high labor and infrastructure costs and rigorous regulatory expectations. Western Europe offers a balance between cost and quality, while Eastern Europe, Asia-Pacific, and Latin America provide more cost-efficient environments, albeit with additional challenges related to regulatory harmonization, logistics, and oversight.

To address rising expenses, sponsors increasingly adopt adaptive trial designs, decentralized and hybrid models, and artificial intelligence (AI)-driven tools for patient recruitment and data analysis. Strategic partnerships with Contract Research Organizations (CROs) and academic institutions further enhance operational efficiency.

5. Post-Marketing Evaluation Methods

Post-market surveillance (PMS) allows manufacturers to monitor the performance of pharmacological therapies by gathering and analyzing real-world usage data. The Commission Delegated Regulation (EU) No. 357/2014 establishes that competent authorities may impose obligations to confirm the efficacy of human medicinal products through post-authorization efficacy studies (PAES) and post-authorization

[9] A. SERTKAYA, T. BELECHE, A. JESSUP, B.D. SOMMERS, *Costs of Drug Development and Research and Development Intensity in the US, 2000-2018*, in *JAMA Network Open*, 7, 6, 2024; M. SCHLANDER, K. HERNANDEZ-VILLAFUERTE, C.Y. CHENG, J. MESTRE-FERRANDIZ, M. BAUMANN, *How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment,* in *PharmacoEconomics*, 39, 11, 2021, 1243–1269.

safety studies (PASS). The results from PAES complement existing efficacy data and could potentially influence the benefit-risk balance of a medicinal product or its accompanying product information. A PAES may be mandated either at the time of marketing authorization (when efficacy concerns can only be addressed post-marketing) or after authorization, if new insights into the disease, clinical methodology, or real-world product usage indicate that previous efficacy evaluations need substantial revision. PASS studies focus on assessing the safety and benefit-risk profile of a medicine, assisting in regulatory decision-making. These studies aim to identify, characterize, or quantify safety risks, confirm the safety profile of a medicine, or evaluate the effectiveness of risk management strategies. PASS studies can be either clinical trials or non-interventional studies.[10]

Additionally, the European Medicines Agency (EMA) oversees Pharmacovigilance within the EU.[11] Pharmacovigilance involves the detection, assessment, understanding, and prevention of adverse effects or other medicine-related problems. The EU's pharmacovigilance system is a collaborative effort between EU Member States, the EMA, and the European Commission. The Pharmacovigilance Risk Assessment Committee (PRAC), part of the EMA, is tasked with assessing and monitoring the safety of human medicines. PRAC prioritizes and evaluates safety signals (i.e., an information suggesting a potential adverse effect caused by a medicine) and issues recommendations based on its findings. These recommendations may include the need for further investigation (e.g., conducting a PASS study), no further action, or regulatory actions such as updating product information.

Post-marketing evaluation highlights the limitations of pre-approval evidence and reinforces the continuity of ethical responsibility beyond authorization. Real-world data introduce new methodological opportunities but also new governance and privacy challenges. This ongoing monitoring underscores the critical role of scientific institutions in managing the complexity of modern clinical research.

6. Scientific Institutions and Their Role in Clinical Trials

Clinical research within the European Union is undergoing a profound transformation following the full application of Regulation (EU) No. 536/2014 on 31 January 2022, which replaces Directive 2001/20/EC[12]. This regulation, known as the EU Clinical Trials Regulation (CTR), introduces a harmonized framework for the assessment and supervision of clinical trials across Member States, aiming to enhance efficiency, promote innovation, and reduce duplication of effort.

The CTR seeks to create a research environment that is both competitive and transparent. Its objectives include facilitating multinational trials, ensuring high standards of participant safety, and promoting public accessibility of clinical trial information. To this end, the European Medicines Agency (EMA) has implemented the Clinical Trials Information System (CTIS), a centralized digital platform designed to manage the submission, assessment, and supervision of all clinical trials conducted within the EU[13]. The

[10] B.M. CESANA, E.M. BIGANZOLI, *Phase IV Studies: Some Insights, Clarifications, and Issues*, in *Current Clinical Pharmacology*, 13, 1, 2018, 14-20.

[11] P. BENINGER, *Pharmacovigilance: An Overview*, Clinical Therapeutics, 40, 12, 2018, 1991–2004.

[12] C. PETRINI, *Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use: an overview*, in *Annali dell'Istituto Superiore di Sanità*, 50, 4, 2014, 317-21.

[13] Z. ZEMLA-PACUD, G. LENARCZYK, *Clinical Trial Data Transparency in the EU: Is the New Clinical Trials Regulation a Game-Changer?*, in *IIC - International Review of Intellectual Property and Competition Law*, 54, 5, 2023, 732–763.

CTIS enhances coordination, supports decision-making among Member States, and ensures the publication of comprehensive trial information for both professionals and the public.

While the EMA manages the CTIS and oversees publication of trial data, the authorization and supervision of individual studies remain the responsibility of national competent authorities. In Italy, these responsibilities are coordinated by the Italian Medicines Agency (AIFA), which serves as the competent authority for clinical trials of medicinal products. Other national stakeholders include the Italian National Institute of Health (ISS), which provides advisory opinions for Phase I studies, the Ethics Committees, responsible for ethical review and approval, and the hospital Directorates General, which manage contractual agreements.

As part of the European network of clinical trial authorities, AIFA plays a central role in aligning Italian procedures with European standards. To support the consistent application of the CTR, AIFA publishes national guidelines and training materials, supplementing resources issued by the European Commission and EMA.

In August 2024, AIFA released new Guidelines on the Simplification and Decentralization of Clinical Trials, published in the Gazzetta Ufficiale on 20 August 2024. Developed by a technical working group established by the Ministry of Health (Decree of 11 January 2024), these guidelines aimed to modernize clinical research processes for medicinal products by simplifying procedures, promoting digitalization, and integrating decentralized elements in line with the European ACT EU (Accelerating Clinical Trials in the EU) initiative. The guidelines address several key areas: the use of third-party service providers in activities related to clinical studies, the reimbursement and compensation for trial participants, the home delivery of investigational medicinal products, and the allocation of costs associated with investigational and auxiliary products.

The National Observatory on Clinical Trials (OsSC) represents another pillar of Italy's research infrastructure. The OsSC manages the authorization process for Phases I–IV clinical trials, provides real-time data on national research activity, and interfaces with the European EudraCT database. It facilitates electronic submissions of clinical trial applications and substantial amendments, ensuring simultaneous transmission to AIFA and the relevant Ethics Committees. At the European level, the OsSC serves as a model for digital workflow integration, promoting transparency, efficiency, and harmonization in clinical research governance.

Through these coordinated institutional efforts (at both the European and national levels) the EU continues to strengthen its position as a global leader in clinical research, combining scientific rigor, regulatory transparency, and patient-centered innovation.

Scientific institutions operate in an increasingly complex governance ecosystem that requires coordination across European and national levels. Their role is no longer limited to administrative oversight but involves strategic adaptation to digitalization, decentralization, and new regulatory paradigms.

A meaningful comparative perspective emerges when considering the different regulatory approaches adopted in the European Union and the United States. While the EU CTR establishes a centralized, cooperation-based governance model through the CTIS and coordinated assessment among Member States, the U.S. Food and Drug Administration (FDA) maintains a more unilateral, agency-driven framework that places stronger emphasis on rapid trial activation and early industry-regulator dialogue (e.g., IND meetings, Fast Track and Breakthrough Therapy designations). Furthermore, unlike the EU system,

which requires ethics review to be integrated at national and regional levels, the U.S. model relies primarily on Institutional Review Boards (IRBs), resulting in more localized ethical oversight. These structural differences shape operational practices: the EU prioritizes harmonization, transparency, and cross-country consistency, whereas the FDA system emphasizes flexibility, speed of development, and earlier regulatory engagement. For scientific institutions, understanding these divergent regulatory cultures is essential, as they influence protocol design, timelines, the integration of decentralized and digital elements, and the overall governance of clinical trial networks[14].

7. Conclusion

In light of the considerations discussed above, it becomes clear that scientific institutions need a comprehensive and balanced approach to manage the growing complexity of contemporary clinical trials. Four interconnected dimensions appear particularly useful in guiding this effort:

- First, scientific integrity remains essential. Institutions must rely on robust study designs, strategies capable of reducing bias, transparent data handling, and validated AI-based tools, where appropriated. Flexibility in methodology, including hybrid and decentralized trial models, has also become increasingly important.
- Equally crucial is ethical and participant protection. As digital technologies, remote monitoring, and algorithmic tools become more common, informed consent procedures must evolve to reflect these realities. Ensuring transparency in algorithmic processes, monitoring for potential bias, and promoting equitable access to participation (especially in decentralized settings) are now fundamental responsibilities.
- A further dimension concerns economic sustainability. Rising costs and logistical demands require institutions to use resources proportionally to the level of risk and complexity involved. Adaptive designs, as well as well-structured collaborations with CROs and academic partners, can help maintain efficiency without compromising scientific rigor.
- Finally, multi-level governance plays a decisive role. Effective alignment between the EU Clinical Trials Regulation, national authorities, and local institutional policies is essential, along with the efficient use of digital platforms such as CTIS and related national systems.

Taken together, these dimensions form a coherent framework that can help institutions navigate the intersection of scientific, ethical, regulatory, and operational challenges.

Clinical trials remain the foundation of biomedical innovation, yet they are increasingly influenced by digital transformation, decentralized approaches, economic pressures, and evolving European legislation. The traditional ethical and deontological principles that have long guided clinical research continue to be relevant, but they must be reinterpreted to align with new technological and methodological contexts.

[14] M. KASHOKI, Z. HANAIZI, S. YORDANOVA, R. VESELY, C. BOUYGUES, J. LLINARES, S.L. KWEDER, *A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why*, in *Clinical pharmacology and therapeutics*, 107, 1, 2019, 195-202.