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REVIEW ARTICLE

Global Regulatory Perspectives on Clinical Data Management: A Comparative Review of Various Regulatory Agencies

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Abstract

Background: Clinical trials are conducted with a set of ethical standards, patient safety measures, and scientific scrutiny. Clinical Data Management Systems have evolved over time, shaped by historical milestones, technological advancement, and international harmonization. **Objective:** This paper aims to analyze real-world evidence and data protection approaches provided by Health Canada, Food and Drug Administration and the European Medicines Agency, and their impact on regulating clinical data. It also discusses modernization of regulatory frameworks. **Methods:** This study is based on empirical legislative documents from international regulatory bodies. Literature from PubMed Central, ScienceDirect, and Google Scholar was consulted to analyze Good Clinical Practice, data integrity, and global data synchronization. **Results:** All agencies reviewed have robust frameworks ensuring data quality, safety, and transparency. Developments include GCP guidelines, electronic data standards (e.g., FDA 21 CFR Part 11), public release policies (e.g., PRCI), and harmonization via ICH guidelines. Real-world evidence (RWE) has expanded post-marketing surveillance and regulatory paradigms. **Conclusion:** Despite regional differences, convergence around international standards and digital systems has strengthened global clinical trial ecosystems. Continuous evolution is needed to adapt to new data sources and safeguard patient welfare.

Keywords: Clinical Trial, Data Management, Drug Approval, Good Clinical Practice, Electronic Health Records

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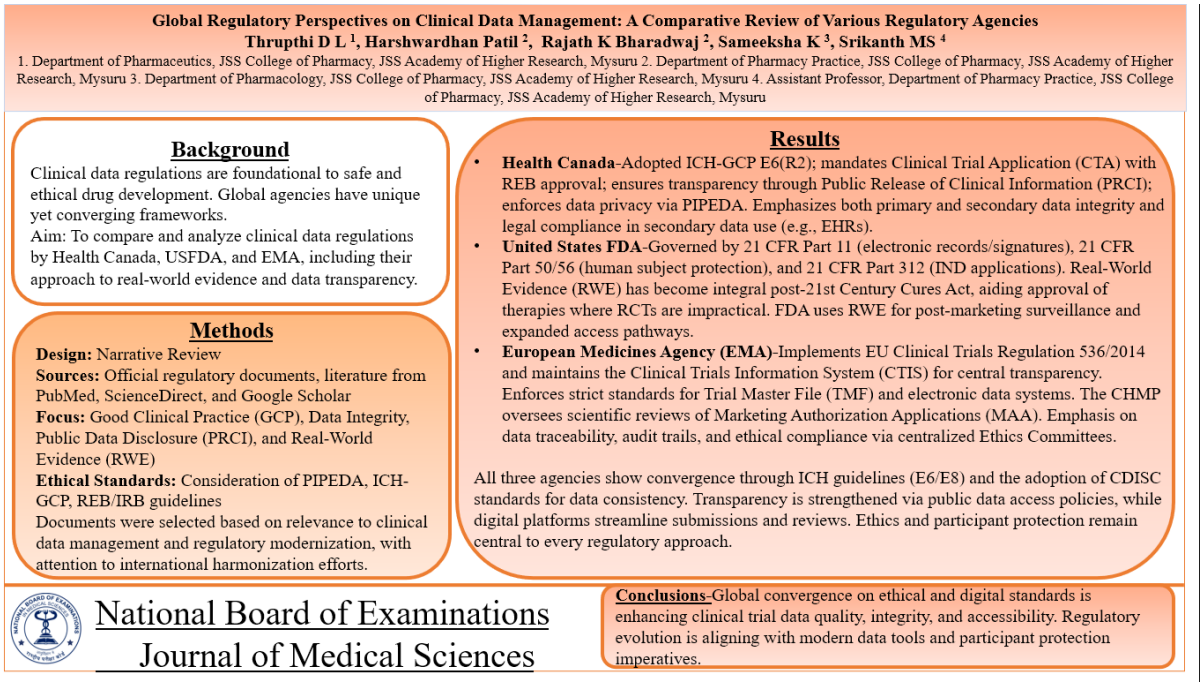
Graphical Abstract



Abbreviations

21 CFR Part 11 – Title 21 of the Code of Federal Regulations Part 11
ADaM – Analysis Data Model
CDISC – Clinical Data Interchange Standards Consortium
CDM – Clinical Data Management
CDMS – Clinical Data Management System
CDSCO – Central Drugs Standard Control Organization
CHMP – Committee for Medicinal Products for Human Use
CTA – Clinical Trial Application
CTIS – Clinical Trials Information System
EDC – Electronic Data Capture
EMA – European Medicines Agency
FDA – Food and Drug Administration
GCP – Good Clinical Practice
ICH – International Council for Harmonisation
IRB – Institutional Review Board
MAA – Marketing Authorization Application
PII – Personally Identifiable Information
PIPEDA – Personal Information Protection and Electronic Documents Act
PRCI – Public Release of Clinical Information
RCT – Randomized Controlled Trial
REB – Research Ethics Board
RWE – Real-World Evidence
SDTM – Study Data Tabulation Model
TMF – Trial Master File
TGA – Therapeutic Goods Administration
USFDA – United States Food and Drug Administration

Introduction

Any approach to encouraging drug development in humans must begin with an understanding of the regulatory conditions governing clinical trials [1]. A clinical trial is designed to produce data to answer a research question, providing evidence to support or refute a hypothesis [2]. Regulatory frameworks extend beyond Good Clinical Practice (GCP); they also provide safeguards that ensure the meaningful and ethical development of new medicines [1].

Clinical Data Management (CDM) is the backbone of modern clinical research, guaranteeing that trial data are complete, reliable, and accurate. Effective CDM goes beyond mere tick-box regulatory compliance; it is essential for ensuring patient safety and maintaining the credibility of trial outcomes.

Lessons from past tragedies, such as the Thalidomide scandal of the 1960s, revealed critical flaws in drug safety protocols. These events reinforced the need for rigorous data oversight throughout drug development [3].

Initially, data were captured using handwritten forms and paper records. In the 1970s, Electronic Data Capture (EDC) systems began automating data entry and reducing clerical errors. By the 1980s and 1990s, standardized digital systems emerged. Organizations like the Clinical Data Interchange Standards Consortium (CDISC) and the International Council for Harmonisation (ICH) were formed to support interoperability and data format standardization.

Modern Clinical Data Management Systems (CDMS) introduced secure storage, audit trails, and automated validation features [4]. Regulatory agencies like CDSCO (Central Drugs Standard Control Organization India), EMA (European Medicines Agency, Europe), and the FDA (Food and Drug Administration United States) now enforce exacting standards for scientific and ethical rigor in trials. Harmonization efforts through the ICH promote global alignment in clinical regulations [5].

1. Health Canada

Evolution of Clinical Data Management Regulations at Health Canada

Health Canada's history with CDM began in the mid-20th century when clinical trials started to take on greater importance. Data management in the early years was unofficial and on paper, with no standardized processes at that point. However, by the late 20th century, regulatory changes were implemented in an effort to strengthen patient safety and improve the quality of data being collected during clinical trials [4]. In Canada, distribution and importation of drugs for human clinical trials are regulated by the Food and Drugs Act and the associated Food and Drug Regulations [6]. In 2001, Health Canada established federal standards for medications used in clinical trials, including adherence to Good Clinical Practice (GCP) guidelines, using Part C, Division 5 of the Food and Drug Regulations under the Food and Drugs Act. Health Canada had already reaffirmed its commitment to participant welfare and clinical trial data quality in 1997 when it adopted the ICH GCP guideline E6(R1) [7].

In order to promote greater effectiveness and calibre of conduct in clinical trials, the ICH guideline was revised to E6 (R2) in 2016. In 2019, Health Canada fully complied with this updated version [7].

Current Regulations and Example Situations

Sponsors must file a Clinical Trial Application (CTA) with Health Canada prior to initiating any clinical trial in Canada. Information about the trial protocol, a risk management strategy, and the qualifications of the participating investigators should all be included in such an application. Every trial must adhere to Division 5 guidelines, Good Clinical Practices (GCP), labelling, and Research Ethics Board (REB) approval. Additionally, sponsors should register trials in WHO-approved registries that are open to the public, such as ClinicalTrials.gov and the Current Controlled Trials Register [8]. Human research is ethically evaluated by the REB, which is required by Health Canada and the Public Health Agency of Canada. It protects research participants by reviewing studies involving biological samples, human subjects, or information pertaining to them [9].

Study Data in Clinical Trials: Regulatory Considerations for Health Canada

Along with the continuous development of clinical trials according to guidelines issued by the regulator, study data are now a part of the regulatory scheme. Study data encompass all the information collected or created in clinical trials, including primary data (specifically collected for the study) and secondary data (derived from external databases or previous studies).

Health Canada's regulatory needs place foremost the collection, processing, and storage of clinical trial data under the Food and Drugs Act and according to Good Clinical Practice guidelines for both data integrity and participant safety.

Sponsors are accountable for high standards of quality, consistency, and completeness for primary and secondary data. Health Canada requires meticulous analysis of each data source to ensure they are accurate, up-to-date, and relevant prior to synthesizing into a study. Additionally, secondary use of data i.e., electronic health records or historical clinical trials—requires extensive analysis to meet the study's individual needs. In cases where secondary data proves insufficient, sponsors must gather primary data to fill in the gaps. Importantly, the use of secondary data must adhere to all legal requirements, particularly those pertaining to participant privacy as specified by the Personal Information Protection and Electronic Documents Act (PIPEDA) [10]. If the research does include referencing external data sources like health records or databases those references must also meet PIPEDA's requirements to keep participant information treated ethically, by law, and in a way demonstrating their rights are respected to their fullest potential [10]. Transparency Through the Public Release of Clinical Information (PRCI).

The responsibility of maintaining clinical data integrity and confidentiality is not only at the process and collection stage but also entails transparency regarding disclosure of this information to the public and the regulatory organizations.

Health Canada openness is reflected in moves like Public Release of Clinical Information (PRCI) that was introduced in March 2019. The move facilitates proactive disclosure of data on approved, unapproved, and withdrawn drug and biologic submissions and Class III and IV medical device applications [11]. Through opening up clinical trial information to the public at time of market authorization,

Health Canada aims to spur public trust, facilitate informed practice by healthcare practitioners and patients, and foster scientific progress. During review, even though the data is maintained under confidentiality, some information can be exempted with a request, so transparency will be maintained under intellectual data protection [12].

2. United States Food and Drug Administration

Key Milestones in FDA Regulatory History

The development of the FDA role during the management of clinical data goes back to early communities that employed medical observation to determine what worked.During the early 20th century, it was trendy to make use of the term "well-controlled" drug trials, which involved the union of clinical and laboratory science. The Federal Food, Drug, and Cosmetic Act of 1938 initially mandated the testing of new drugs for safety prior to sale, enabling the FDA to review pre-clinical and clinical information prior to approval. The law also provided the FDA with the right to delay or prevent the marketing of a drug when additional data were required. After the 1961 international drug debacle, the 1962 Drug Amendments ensured that not just safety, but also "substantial evidence" of efficacy under clinical tests would be required for drug approval. The FDA took on the role of determining what standards were to be employed in drug testing, which fortified the need for "adequate and well-controlled" studies to gain approval [13].

Present Day Food and Drug Administration Regulations

Existing guidelines established by the FDA concentrate on safety, effectiveness, and integrity of clinical information, responsive to evolution in clinical trial design, technology, and international standards. The guidelines provide new guidance on conduct of clinical research with protecting the participants and ensuring integrity of the data.

GCP prescribes internationally agreed standards for the design, conduct, and reporting of trials in relation to the ethical considerations. It is focused on data quality and ethical adherence. With advancements in technology, the FDA published the Electronic Records and Electronic Signatures regulation (21 CFR Part 11) in an effort to provide standards for reliable and valid electronic records and signatures. This was due to the growing application of electronic systems in FDA-regulated activities. Part 11 was enacted on August 20, 1997, and it makes electronic technologies available to use while protecting public heal [14]. It provides the guidelines for the application of controls like audits, system verifications, audit trails, and electronic signatures. In 2003, the FDA issued guidelines, and in 2007, an authoritative version was published to help provide clarification to the use and application of Part 11. These are applicable to most industries like the drug firms, medical device firms, and biotechnology firms [15].

Protection of Human Subjects (21 CFR Part 50) mandates that human subjects provide informed consent, being aware of the risks and benefits of active involvement. The regulation prioritizes participants' rights and welfare in the research process. Institutional Review Boards (21 CFR Part 56) govern the ethical aspects of the clinical trial. They evaluate and approve study protocols to ascertain that the research is

carried out ethically and risks to participants are kept at a minimum. In America, the Investigational New Drug (IND) Application, which is regulated by 21 CFR Part 312, sets forth the procedure for filing clinical trial results on new drugs [16].

Use of Real-World Evidence (RWE) in USFDA Approvals

Real-World Evidence (RWE) originates from traditional registry-based research, which has been around for many decades. However, the term "real-world evidence" only gained widespread popularity in the early 2000s. In 2004, the first important practical example of RWE could be found in the study of lamotrigine for bipolar disorder treatment, which indicated a significant milestone towards RWE potentially being a meaningful contributor to clinical research. In 2016, the passage of the 21st Century Cures Act prompted a major shift indicating the U.S. FDA intended to actively incorporate RWE into its regulatory decision-making processes. This was a tipping point and officially solidified RWE in the chronicles of history as an integral mechanism by which new health care policies and avenues of clinical practice are developed. [17] RWE has since gained traction as an evolving and evolving viable body of knowledge with insights on how effective interventions work in routine clinical use as opposed to tightly-controlled clinical trial settings. RWE facilitates questions about how effective treatments are prescribed, how effective they are billed in routine clinical practice, and ad adverse effects could emerge over time. RWE can be gathered from various types of sources including observational studies, pragmatic trials, electronic health data, and even claims data to provide a full and richer impression of treatment experiences [18].

Where conventional randomized controlled trials (RCTs) are not possible based on ethical or practical limitations, the FDA has increasingly relied on RWE to inform its regulatory actions. Indeed, between 2017 and 2022, RWE was involved in a broad variety of assessments—demonstrating its growing role in the regulatory science [19] ecosystem.

In total, RWE has become a critical resource for the FDA, enabling meaningful alternatives to conventional trials and expanding patient access to cutting-edge therapies—particularly where there is great unmet medical need [20].

3. European Agency Regulation of Clinical Trials

Clinical trials are critical to the creation of new therapies and the continuous advancement of healthcare. In Europe, the regulation of these trials has undergone significant change through the years, all directed at establishing a more harmonized system among EU member states—yet maintaining participant safety and the validity of clinical data. This article examines the historical milestones, current regulatory practices, mechanisms of oversight, and data management procedures employed by European regulatory authorities [19].

Historical Context

The sequence of tragic and dramatic incidents that caused Europe to start thinking about the regulation of clinical trials, is impacted by the thalidomide incident in the 1960s where thousands of babies were born with birth defects due to the absence of rigorous safety testing [20].

In 1965, the countries of the European Union implemented their pharmaceutical law with the adoption of Directive 65/65/EEC. For the first time, it was written that no drug could be offered to the public prior to the approval of the national authority of that country. This was the watershed legislation that cemented public health control by creating regulations that all drugs must be proven safe and efficacious before being approved [21]. Prior to 2001, each EU Member country had its own regulatory and approval process for clinical trials resulting in a fragmented environment that made multinational research difficult to organize and even more difficult to implement. In 2001, the European Commission addressed these problems with the European Clinical Trials Directive (Directive 2001/20/EC) [23].

Clinical Data Regulation and Management

Regulatory control in clinical trials has been shaped by critical historical, ethical, and technological milestones. The global efforts, though fragmented, have worked collectively to catalyze developments in data integrity, transparency, and harmonization of clinical data standards. Such milestones from legislative reformations to electronic innovations are enumerated in Table 1 that presents an integrated overview of regulatory transformations which influenced Clinical Data Management practices globally. Good clinical data management is crucial in order to ensure a credible and dependable result from a clinical trial. To assist with this, the European Medicines Agency (EMA) published the "Guideline on Computerised Systems and Electronic Data in Clinical Trials" specifying detailed guidelines about the following topics:

- The use of computerised systems in the clinical trial process
- The data collection and processing of electronic data
- Data quality, accuracy, and reliability measures
- Provisions meant to protect the rights, dignity, safety, and well-being of trial subjects.

The guideline gives considerable emphasis to data integrity during each step of a clinical trial process from the initial collection of first-hand data to final long-term storage [24].

Additionally, it lays out precise specifications for system validation, accurate data entry, and audit trails to monitor data modifications. These rules are meant to support the integrity of the trial data and participant safety by guaranteeing that electronic records are always accurate, comprehensive, and secure. Furthermore, the European Medicines Agency (EMA) has released final guidelines regarding the structure, administration, and preservation of the Trial Master File (TMF), a crucial part of clinical trial documentation.

According to the guidelines, the TMF must contain all the documentation needed to demonstrate how the trial was carried out and how the data were handled, and it should be easily available for regulators to review. The TMF needs to have a thorough version history, good document identification, and traceability of any updates or modifications, regardless of whether it is stored electronically or on paper. These procedures support the clinical trial process's accountability and transparency [25]. Current Regulations and

the Most Important Laws in European Clinical Trials To safeguard the rights and welfare of those who take part in clinical trials, the European Union (EU) has established a strong regulatory framework [25]. The ICH E6 Good Clinical Practice (GCP) guideline, as implemented by the European Medicines Agency (EMA), gives clear and comprehensive guidance to ensure the protection of human subjects during clinical trials. It sets forth sponsors', investigators', and Ethics Committees' specific responsibilities and makes sure that trial subjects' rights, safety, and well-being are afforded maximum attention at every stage of research [26].

Ethics Committees (Institutional Review Boards)

Within the EU, Ethics Committees have a significant role to play in guiding clinical trials. A trial, prior to commencement, will need to have a favorable opinion from an Ethics Committee regarding whether the ethical issues of a trial are deemed acceptable, i.e., evaluating the informed consent process for adequacy, the risk-benefit and human participant right safeguard. The Clinical Trial Regulation harmonizes the function of and the duties of Ethics Committees in member states and provides consistency in the ethical assessment process [27].

New Drug Application (Marketing Authorization Application)

In the EU, the parallel procedure to the New Drug Application (NDA) in the US is the Marketing Authorization Application (MAA). Pharmaceutical firms are required to file an MAA with the EMA in order to be authorized to market a new drug product.

The filing must contain extensive clinical trial data that confirm the quality, safety, and effectiveness of the product. The EMA's Committee for Medicinal Products for Human Use (CHMP) reviews the filing on a scientific basis and makes a recommendation regarding whether or not the drug should be approved [22].

Principal Legislative Regulations

1. Clinical Trials Regulation (EU) No 536/2014

This directive is a significant move toward harmonizing the way clinical trials are evaluated and regulated across the EU. Its primary aim is to simplify the approval process among member states while maintaining maximum transparency and the highest level of safety standards for trial participants. Perhaps its most prominent feature is the establishment of a centralized EU portal and database, which will make trial information more readily available to regulators and the public.

2. Directive 2001/20/EC – The Clinical Trials Directive

Enacted in 2001, this was the initial EU-wide legislative package specifically aimed at clinical trials. Although most of its provisions have since been updated by the new Regulation (EU) No 536/2014, certain aspects continue to be in place throughout the transitional period. Accordingly, it continues to influence clinical trial practice in some situations, especially for those trials initiated prior to the coming into effect of the new regulation.

3. ICH E6(R2) – Good Clinical Practice (GCP) Guideline

This internationally accepted guideline sets out both scientific and ethical requirements for designing, conducting, recording, and reporting clinical trials in human subjects. Adherence to GCP

guidelines ensures that the rights, safety, and well-being of participants are safeguarded at all times, and assists in ensuring the credibility and integrity of the data produced [26].

These rules and regulations collectively ensure that clinical trials in the EU are conducted ethically, with robust human subject protections, and under stringent scientific standards for the approval of new medicinal products.

Conclusion

The development of European clinical trial regulation reflects a bias towards harmonization of procedure, increased transparency, and protection of participants' safety and rights.

The adoption of the Clinical Trials Regulation (EU) No 536/2014 and launch of the CTIS mark an important step toward a more efficient and harmonized system.

In parallel, the EMA computerized system and data management rules put the role of data integrity and safeguarding participant safety in the era of electronic technology in stark relief.

As the environment of clinical research continues to change, European regulatory authorities remain devoted to promoting an environment conducive to scientific progress alongside the strictest ethical and quality standards.

Table 1. Chronology of Global Regulatory Milestones in Clinical Data Management. This table presents a chronological summary of key global events and regulatory initiatives that have significantly shaped the evolution of Clinical Data Management (CDM). It includes the respective regulatory bodies and the major outcomes associated with each milestone.

Year	Event	Regulatory Body	Impact on CDM
1962	Kefauver–Harris Amendment	U.S. FDA	Required drug manufacturers to demonstrate the effectiveness and safety of their drugs prior to approval [28].
1996	ICH-GCP (E6) Guidelines Adoption	U.S. FDA, EMA, TGA, Health Canada	Established unified standards for designing, conducting, recording, and reporting clinical trials [29].
1997	21 CFR Part 11 Implementation	U.S. FDA	The U.S. FDA Set criteria for electronic records and electronic signatures, ensuring their reliability and equivalence to paper records [30]

2001	EU Clinical Trials Directive (2001/20/EC)	EMA	Harmonized the regulation of clinical trials across EU member states, emphasizing the protection of clinical trial participants [31].
2003	Adoption of CDISC Standards	U.S. FDA, EMA, TGA, Health Canada	Promoted the use of standardized data formats (e.g., SDTM, ADaM) for the submission of clinical trial data [32].
2004	Guidance on Electronic Records and Signatures (21 CFR Part 11)	U.S. FDA	This guidance provided a framework for the use of electronic records and signatures in clinical trials [33].
2014	EU Clinical Trials Regulation (536/2014) Approval	EMA	Aimed to streamline and harmonize the assessment and supervision processes for clinical trials throughout the EU [34].
2019	TGA's Priority Review Process Implementation	TGA	Established an expedited pathway for the evaluation of certain prescription medicines, reducing approval times [35].
2020	Health Canada's Public Release of Clinical Information Initiative	Health Canada	Launched a policy to increase transparency by making clinical information from drug submissions and medical device applications publicly accessible [35].

Abbreviation: FDA: Food and Drug Administration (USA), EMA: European Medicines Agency, TGA: Therapeutic Goods Administration (Australia), CDISC: Clinical Data Interchange Standards Consortium, ICH: International Council for Harmonisation, GCP: Good Clinical Practice PRCI: Public Release of Clinical Information.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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