Borneo Journal of Pharmacy
Vol 6 Issue 1 February 2023
Pages 93 – 109

https://journal.umpr.ac.id/index.php/bjop/article/view/3263
DOI: https://doi.org/10.33084/bjop.v6i1.3263
e-ISSN: 2621-4814

Article Review

Clinical Trials: The Role of Regulatory Agencies, Pharmacovigilance Laws, Guidelines, Risk Management, Patenting, and Publicizing Results

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Keywords:
Clinical trial
Pharmacokinetics
Pharmacovigilance laws
Regulatory authorities
Risk management

Abstract

The research carried out to find a better treatment, improve healthcare, and benefit the current medical practice is termed clinical research. Clinical trial includes the pharmacodynamics (mechanisms of action of a new drug), pharmacokinetics (drug metabolism inside the body), therapeutics (efficacy of the drug), and adverse effects (safety of the drug) of the novel medical products. Clinical research is a process that involves human subjects and their biological specimens. The clinical trial is a meticulously planned protocol-based study of a drug/device to discover a new/better way to prevent, diagnose, and treat a disease/illness. Considering the involvement of both healthy and diseased people in clinical trials, the regulatory authorities have a significant role in the processes involving the conduction of clinical research and carefully evaluate their potential implications on humans. Because clinical trials are usually aimed at assessing the safety and efficacy of novel pharmaceutical compounds and medical devices, pharmacovigilance laws and risk management assume increased significance while conducting clinical research/trials. In this review, we attempt to discuss the regulatory authorities' roles in different geographical regions, including the United States of America, The European Union, and India. We also focus on the importance of pharmacovigilance laws and risk management during clinical trials.

Received: February 9th, 2022
1st Revised: January 22nd, 2023
Accepted: February 20th, 2023
Published: February 28th, 2023

INTRODUCTION

The importance of the need for clinical research, clinical research types, groups, and phases of clinical research has assumed increased significance. Clinical research studies are undertaken to assess the safety and efficacy of a drug, vaccine, device, or medical diagnostic test assay in treating, preventing, diagnosing, and controlling diseases[1,2]. In most instances, clinical research is carried out to satisfy unmet medical needs that include discovering a treatment for a newly emerged microbial species, like the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)[3-5]. They can also be conducted to find treatment for an existing illness with no/limited therapeutic options, like various types of cancers (breast cancer, arthritis,

How to cite: Kandi V, Vadakedath S, Addanki PS, Godishala V, Pinnelli VB. Clinical Trials: The Role of Regulatory Agencies, Pharmacovigilance Laws, Guidelines, Risk Management, Patenting, and Publicizing Results. Borneo J Pharm. 2023;6(1):93-109. doi:10.33084/bjop.v6i1.3263

and others)[6,7]. The international clinical trial registry platform (ICTRP) provided by the World Health Organization (WHO) aims to increase awareness of the need to register the clinical trial, improve the comprehensiveness, completeness, and accuracy of registered clinical trial data, enable access, and ensure data utilization[8].

Clinical research types include observational studies and experimental/analytical studies. Observational studies do not involve any intervention and depend majorly on the collection of data and its analysis. Experimental studies are considered the gold standard, and intervention is integral to such research, including cases and control subjects[9]. Two groups of clinical research trials include comparative and open-label clinical research trials. The comparative clinical research trial includes the case group (who receive the test drug) and the control group (who receive a placebo/dummy). Such research is carried out as a randomized, double-blinded clinical trial where neither the investigator nor the patient/participant knows about the kind of intervention. This helps neutralize any bias which may influence the study results. Different types of randomizations in clinical trials[10-15], types of clinical research trials, phases of clinical trials[16-20], their roles, and the nature of studies are elaborated in **Table I** to **III**, respectively.

Table I. Different types of randomizations in clinical trials

Randomization type	Functions
Simple randomization	The participants are assigned to a case, or a control group based on flipping coin results/computer assignment
Block randomization	Equal and small groups of both cases and controls
Stratified randomization	Randomization based on age of the participant and other covariates
Co-variate adaptive randomization	Sequential assignment of a new participant into a group based on the covariates

Table II. Types of clinical research trials and their functions

Clinical trial type	Functions
Treatment	New/improved therapeutics
Prevention	Reduce/prevent disease, includes healthy participants
Early diagnosis/screening	Minimizes the risk of diseases, includes, both the diseased and healthy subjects
Confirmation of diagnosis	To diagnose the disease accurately in infected population
Management (quality/support)	Minimize the adverse effects of the drugs, benefits of nutrition

Table III. Phases, types, and nature of a clinical trial study

Phase, subtypes of clinical trial	Type of study	Nature of study
Phase 0	Exploratory	Examines too low concentrations (micro dosing) of drug for less time. Study the pharmacokinetics and to determine the dose for phase I studies. Presently done in animals and future human micro dosing studies are expected
Phase I Phase Ia Phase Ib	Non-therapeutic trial	Around <50 healthy subjects are recruited. Establishes safe dose range, the maximum tolerated dose and examines the pharmacokinetic and pharmacodynamic effects Single centre studies Phase Ia: SAD-single ascending dose, MTD-maximum tolerated dose. Duration of one week including 6-8 groups of 3-6 participants Phase Ib: MAD-multiple ascending doses, and the dose is gradually narrowed down. Three groups of 8 individuals each
Phase II Phase IIa Phase IIb	Exploratory trial	Recruiting around 5-100 patients of either sex. Examines the effective dosage and the therapeutic effects in patients It decides the therapeutic regimen, drug-drug interactions. Multicentre studies Phase IIa: decides the drug dosage, includes 20-30 patients, and takes up to weeks/months Phase IIb: studies dose response relationship, drug-drug interactions, comparison with a placebo
Phase III	Therapeutic confirmatory trial	More than 300 patients (up to 3000) of either sex are recruited in this study, multicentric trials. Pre-marketing phase Examines the efficacy and the safety of the drug Comparison of test drug with the placebo/standard drug Adverse drug reactions/adverse events Initiate the process of New Drug Application (NDA) with appropriate regulatory agency like the Food and Drug Administration (FDA)
Phase IV	Post-approval study	After approval/post-licensure and post-marketing studies/surveillance. Following up of the patients for an exceptionally long time for potential adverse reactions and drug-drug interactions

Clinical trials and research are undertaken to satisfy unmet medical needs, and this assumes increased significance in the era of antibiotic resistance and the emergence and re-emergence of both contagious and non-contagious diseases[21]. Clinical research demands the practice of ethical principles while conducting a clinical trial. It becomes a real challenge to conduct a clinical trial during an epidemic/pandemic situation[22]. An emergency-like situation arises due to the lack of an approved drug against a novel microbial infection, as noticed in the recent pandemic of SARS-CoV-2/Coronavirus disease-19 (COVID-19)[23]. It is interesting to note that the first description of clinical trials dates to 550 BC, and several ancient instances discuss and describe the process of a clinical trial. It was noted that the clinical trials started with dietary interventions (legumes and lemons), and after hundreds and thousands of years, we reached the status where we discovered and manufactured drugs[24].

REGULATORY REQUIREMENTS IN CLINICAL RESEARCH

Clinical research and drug trials involve human participants and pose significant ethical concerns. History has witnessed many such instances where human participants were recruited in a drug trial, resulting in significant morbidity and mortality. Given such experiences, there needed to be regulatory bodies overseeing the clinical trials involving human participants[25]. The regulatory bodies and the episodes of unethical practices that occurred worldwide are depicted in chronological order in **Figure 1**.

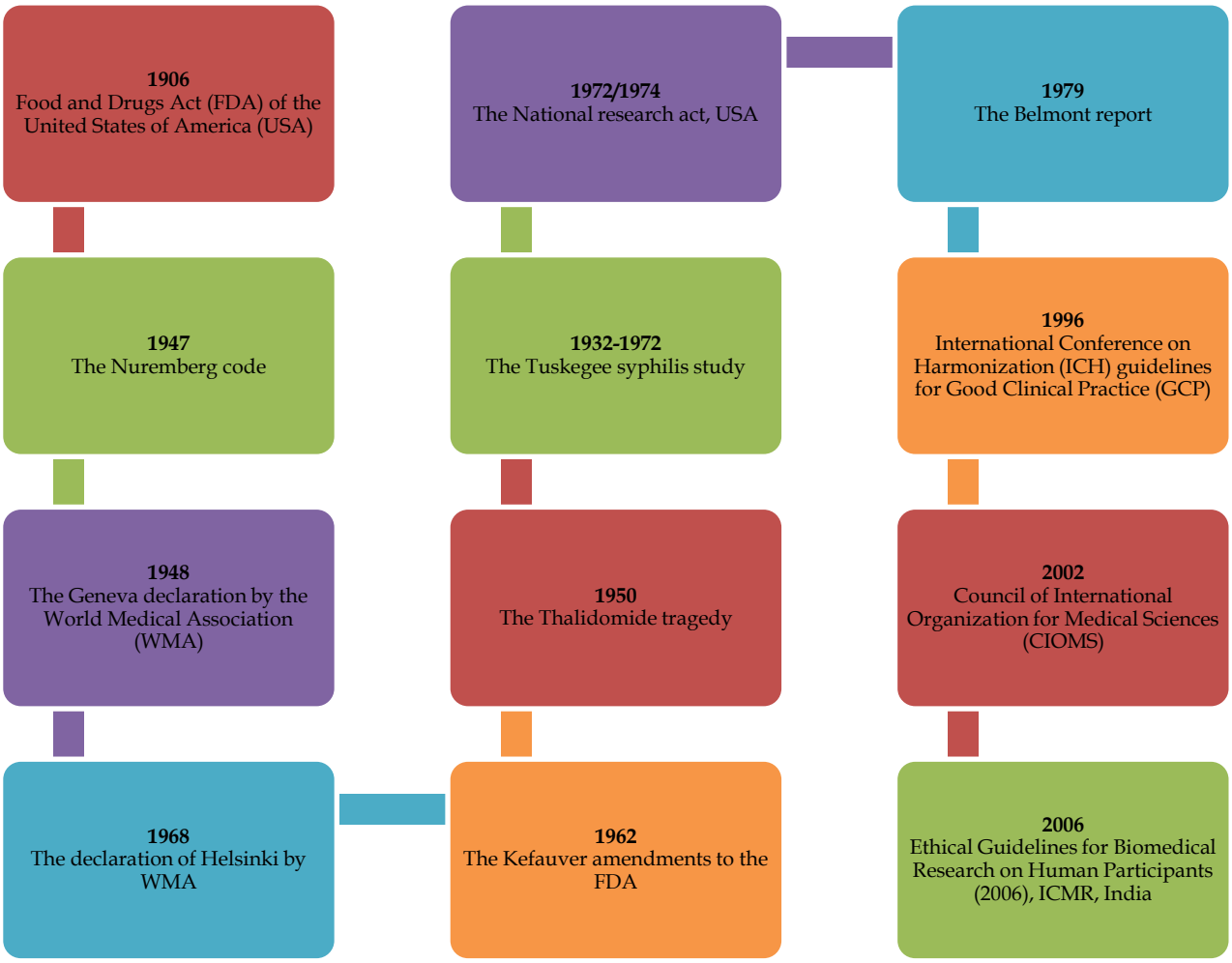

Figure 1. Chronological depiction of unethical practices and the emergence of ethical principles in clinical research

After the Nazi experiments on prisoners, the Nuremberg Code was implemented on August 19th, 1947. This code made voluntary consent an essential element while conducting clinical trial research. The requirement for voluntary consent protects the rights of participants against deceit. It was also made mandatory that the research on animals is performed

before human trials and that the trial will not lead to death or permanent injury to study participants[26]. Given several reports of unethical practices related to clinical trials and research in the past, it was imminent that a regulatory body is present which takes responsibility for all the ethical concerns related to clinical research with special reference to patient safety and well-being. The first regulatory recommendation was the Nuremberg Code (August 9th, 1947), followed later by the WMA's Declaration of Helsinki (June 1964). In 1974, the National Research Act was passed by the US Congress, which aims to protect human subjects for biomedical and behavioral research. The regulations under this act included an institutional review board (IRB) and 45 CFR46 (Title 45 Code of Federal Regulations Chapter 46)[27].

The objectives of regulatory bodies in satisfying ethics concerns include safeguarding the participant's dignity, justice, equality, protection against exploitation and injury/harm, truth, and trust. They also promote the importance of acting appropriately in each situation and provide necessary and strong reasons to support the act. The first ethical concept in medical practice dates to 400 BC, when Hippocrates proposed an oath that is deemed to be followed by all medical practitioners. Although the Belmont Report was introduced on April 18th, 1979, its proposed principles include respect for the persons (informed consent), beneficence (causing no harm), and justice, which remains the mainstay even today for conducting clinical trials. While conducting a clinical trial, the first and foremost concern which needs to be addressed by the stakeholders is the assurance of the safety and well-being of the study participants[28]. A previous study[29] highlighted the significance of federal rules that govern participants' rights and safety. In a recent development, the ICMR prescribed guidelines for clinical research during the SARS-CoV-2 pandemic. Along with the basic principles, twelve more general principles were added. These include principles of essentiality, voluntariness, non-exploitation, social responsibility, ensuring privacy and confidentiality, risk minimization, professional competence, maximization of benefit, institutional arrangements, transparency and accountability, the totality of responsibility, and protection of the environment[30].

GOOD CLINICAL PRACTICE GUIDELINES IN CLINICAL RESEARCH

Good clinical practice (GCP), as the name suggests, are specific guidelines prescribed for the physicians involved in patient treatment, management, and research involving humans. GCP statute dates to the Hippocratic oath, where the physicians take an oath that they do not harm the patients. Due to increasing complexities concerning patient management and scientific research involving human subjects, GCP guidelines have been formulated more elaborately. The GCP guidelines cover almost all aspects of clinical research, including design, conduct, termination, audit, analysis, reporting, and documentation of clinical trials among human subjects. The GCP guidelines ensure that clinical trials on humans are conducted after considering the rights and safety of the study subjects and that the data generated through the trial is reliable and authentic[31].

The systematic and regulated process of conducting clinical research that results in reliable data, which helps make public health-related decisions and improves health care, is called the GCP. The GCP guidelines were framed after considering the recommendations of the WHO, ICH, USFDA, European GCP guidelines, and the ethical guidelines for biomedical research involving human subjects of the Indian Council for Medical Research (ICMR). The terminologies included in the GCP guidelines[32-34], which form the clinical research process, are shown in **Tables IV** to **VII**.

Table IV. Definitions and Terminologies used in clinical research/trials

Terminology	Function
Clinical trial	A systematic study of a novel pharmaceutical product in humans including its pharmacodynamics/ pharmacokinetics, adverse effects, safety and/or efficacy
Comparator product	A drug/placebo used to compare the pharmaceutical product
Confidentiality	The privacy of the human participants in a clinical trial
Act	Drugs & Cosmetics Act 1940 (23 of 1940)
Adverse Event (AE)	Medical consequences (symptoms) of the drug therapy
Adverse Drug Reaction (ADR)	Unintended consequence of the treatment with trial drug
Type A ADR	Dose dependent ADR, which is reversed with reducing/withdrawing the drug
Type B ADR	ADR that was not predicted
Serious adverse event (SAE)	The AE or an ADR that results in death, permanent disability, and hospitalization, including birth defects
Escape treatment	A therapeutic intervention in the control subjects (placebo) for symptomatic relief

Table V. Definitions and roles of major clinical trial bodies

Terminology	Function
Sponsor	An individual or an institution which takes the responsibility of initiation, conduction, management, and financing the clinical trial/research
Principal investigator	An individual, qualified adequately, who oversees the clinical research at the trial site and co-ordinates with the investigators at other trial sites in case of multi-centric trials
Investigator	A qualified person who is responsible for trial at the site
Co-investigator	A qualified person who is designated to share the responsibilities of an investigator, they are usually a part of multi-centric studies
Study subject	A person who volunteers to participate in a clinical trial
Monitor	A person designated by the sponsor to ensure the trial is conducted in accordance with the protocol, and the standard operating procedures (SOP's)/Contract/clinical research organization (CRO)
CRO	The organization chosen (contract) by the Sponsor to make sure that the research trial at the site is conduct scientifically.
Ethics committee	A committee which works independently, and which approves the clinical research after a thorough evaluation
Audit	The independent body which verifies/inspects trail procedures are done according to protocol, and data validity

Table VI. Documents and their significance in the clinical research

Terminology	Function
Contract	A written document which is dated and signed by the sponsor, the investigators, and the institution
Protocol	A document that details the background, aims, objectives, design, methodology, and other relevant considerations of the clinical trial
Standard operating procedures (SOP's)	The documents which delineate the process to maintain uniformity related to the conduction, recruitment of study participants, data collection and evaluation of data
Case record form (CRF)	A systematically designed document to collect the data with respect to the clinical trial subjects record data accurately, minimize manipulation, and ease of verification, and audit
Informed consent	A document signed by the study participants which confirms the voluntariness
Investigator's broacher	A document delineating the justification for the proposed study, also having the clinical, and non-clinical details of the investigational product
Source data/Raw data	All certified and verified documents related to the study participants that includes laboratory data like the X-ray film, hospital records, and others
Final report	A document which comprehensively describes the study that includes the materials, statistical methods, results, and final inputs from the investigator
Contract	A written document which is dated and signed by the sponsor, the investigators, and the institution
Protocol	A document that details the background, aims, objectives, design, methodology, and other relevant considerations of the clinical trial

Table VII. Important activities and their functions in a clinical trial

Terminology	Function
Protocol amendments	A document stating modification in the protocol, which must be signed by the investigator and relevant parties, and approved by the ethics committee
Quality Assurance (QA)	The system/process developed to make sure that the clinical research is conducted in accordance with GCP guidelines
Quality Control (QC)	A fool proof check system that ensures that all the elements (planning, conduction, data collection, evaluating, and reporting) of a clinical trial are conducted under controlled environment
Regulatory authority	The central drugs standards control organization of India, the food and drugs administration of the USA are a few examples of regulatory authorities which approves clinical research and the pharmaceutical product
Validation	The process undertaken to confirm the authenticity of a clinical trial, and all the elements in it to establish the reliability of the results
Binding/masking	Type of intervention, double blind, single blinded, remove bias
Randomization	Assigning the patients into the study and control groups to minimize bias
Multi-centric studies	A clinical trial which is conducted at multiple sites but is done in accordance with the same protocol
Non-clinical trial study	A study that does not include human subjects
Non-therapeutic study	A study that does not result in any clinical benefit to the subjects

Clinical research results are meant to be used for providing better health care. Statistics and their application assume increased significance in assessing and analyzing the data generated from clinical research. Clinicians need to understand the statistics to evaluate the current study results generated from evidence-based medicine and apply them in regular clinical practice[35]. A previous research study attempted to evaluate the clinician's abilities to understand the statistical concepts, knowledge of biostatistics, and familiarity with the statistical methods. It was observed that 75% of the physicians had better knowledge of statistical methods, which helped them to correctly interpret and understand the evidence-based research results and apply them while treating the patients[36].

REGULATORY AUTHORITIES FOR PHARMACEUTICAL IN THE UNITED STATES

Clinical research or a trial must be done after adhering to the regulatory requirements, which are majorly done to ensure the reliability of the clinical trial results/data. The regulatory agency which is responsible for protecting human health by regulating/supervising the production and marketing of several products in the united states of America is the Food and Drugs Administration (FDA). It is the oldest consumer protection regulatory agency. The FDA regulates food (human and animal), tobacco, pharmaceutical drugs (prescription and on-the-counter drugs), medical devices, and cosmetics. The president of the USA appoints the commissioner of the FDA and reports directly to the secretary of health and human services[37]. The FDA has its headquarters in Maryland and has foreign offices in India, Belgium, Costa Rica, Chile, China, and the United Kingdom. First, federal laws were enforced against the use of harmful food colors, misbranding foods, and food adulteration. In 1820, the first publication on the regulations concerning pharmaceutical drugs was published as US Pharmacopeia[38].

Although the US had a regulatory agency that looked after food and pharmaceutical products from the early 1800s, the original FDA was passed on June 30th, 1906, during President Theodore Roosevelt's leadership. From the year 1935, the USA started publishing the federal register. In 1999, the US FDA introduced the online portal called https://clinicaltrials.gov/, a registering agency for nationally funded and privately financed clinical research. The Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) was passed in 2013. It regulates the programs under the Public Health Service Act and the Food, Drug, and Cosmetic (FDC) Act concerning public health security and all-hazards preparedness and response. The Drug Quality and Security Act (DQSA) was enacted in 2013, which regulates the electronic and interoperable system for prescription drugs. The federal register, which delineates the permanent rules and regulations, is published as the Code of Federal Regulations (CFR), which consists of 50 titles, each divided into chapters, parts, subparts, and sections, and is updated yearly. The regulatory requirements constitute laws and rules for research approval, registration, licensure, manufacture, handling, storing, import, export, and distribution or sale[39].

Although regulatory authorities are functioning worldwide, a recent research study has highlighted the need for increased assistance regarding the quality of the probiotics available in the market[40]. It is the responsibility of regulatory agencies like the US FDA to protect people's safety and welfare. It was suggested that a comprehensive information base is to be established which may provide reliable information and facilitate the decision-making process of regulatory agencies[41].

REGULATORY AUTHORITIES FOR PHARMACEUTICAL IN EUROPEAN NATIONS

The European Union (EU) is not single but a consortium of many countries (27 member states). The EU constituted the European Medicines Agency (EMA), which evaluates medicinal products. It was established in 1995 with the aid of the EU, pharma industries, and member states' contributions. The EU contributes one third of the new pharmaceutical products introduced worldwide. The EU protects and promotes public and animal health by evaluating and supervising medicinal products. It provides technical guidance and scientific advice to the sponsors concerning medicinal products, including biologics, advanced therapeutics, and herbal medicinal products[42]. The EU medicines agency work process is shown in **Figure 2**.

The EU manufacturers follow a centralized approach to obtain permission from marketing authorization (MA) valid in all EU and European Economic Area (EEA)-European Free Trade Association (EFTA) states (Iceland, Liechtenstein, and Norway). Also, some committees include Committee for Medicinal Products for Human Use (CHMP), Committee on Orphan Medicinal Products (COMP), Paediatric Committee (PDCO), Committee for Advanced therapy medicinal products (ATMPs), and Pharmacovigilance Risk Assessment Committee (PRAC). The drug filing process in the EU happens through the National procedure, Mutual recognition procedure (MRP), Decentralized procedure (DCP), and Centralized procedure (CP).

Because of no uniform data source, most European countries rely on the quantitative data on health services provided by the World Health Organization (WHO) Regional Office for Europe's European Health for All Database. Other reliable sources of data are derived from the national statistical offices, Eurostat, the Organisation for Economic Co-operation and Development (OECD), International Monetary Fund (IMF), and the World Bank's World Development Indicators[43]. A systematic and strategic approach, including direct and indirect regulatory policies, was done to shape pharmaceutical care

and improve patient access to better healthcare/medicine. This was implemented by a group of 16 countries where regulatory mechanisms were applied to contain pharmaceutical expenditure and ensure quality and efficiency in pharmaceutical care[44].

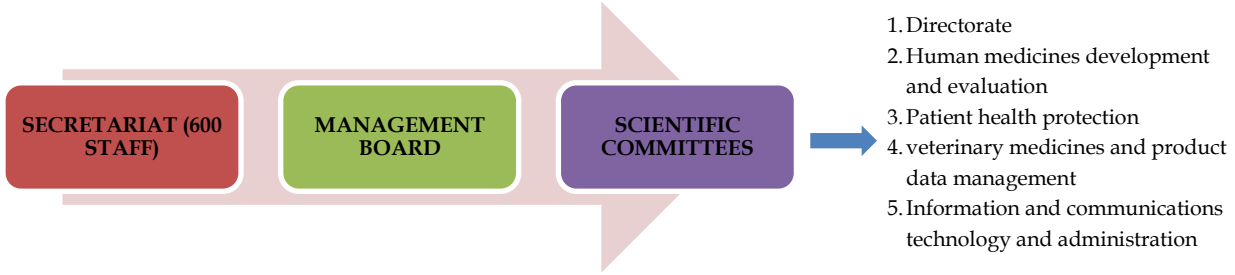

Figure 2. The EU medicines agency work process

REGULATORY AUTHORITIES FOR PHARMACEUTICAL IN INDIA

Pharmaceutic products and related matters in India are regulated by the central drugs standards control organization (CDSCO), headed by the director-general of health services under the Ministry of Health and Family Welfare founded under the Drugs and Cosmetics Act (DCA 1940). The national capital Delhi is where the CDSCO's headquarters is located, with six other cities being identified as zonal offices, including Mumbai, Chennai, Kolkata, Ghaziabad, Hyderabad, and Ahmedabad. Besides, Bangalore, Jammu, and Chandigarh function as sub-zonal offices; the other 11 offices are located at seaports/airports across the country. CDSCO has six offices as drug testing centers in Kolkata, Mumbai, Chennai, Guwahati, Chandigarh, and Hyderabad. The Drug Controller General of INDIA (DCGI) functions to regulate the clinical trials in India and issues licenses to import drugs[45].

The clinical trial regulations and guidelines are in function through the Amended (2013) Schedule Y of DCA, 1940. The CDSCO publishes the GCP guidelines, and the Indian Council for Medical Research (ICMR) publishes the guidelines for ethical principles of biomedical research. Also, the clinical trials conducted in India are registered at the Clinical Trial Registry of India (CTRI). To minimize the disparities and increase the efficiency of the regulatory authority concerning clinical research, the CDSCO made an amendment that ensures registration of the ethics committees, registration of clinical research organizations (CROs), audio-visual recording of informed consent, letter of permission to conduct a clinical trial, and reporting/recording SAE's and study participants redressals (compensation)[46]. The central office/headquarters and the zonal offices function in a specified manner, as shown in **Table VIII**.

Table VIII. The functions of central office/headquarters and the zonal offices of CDSCO

Functions of central office/headquarter	Functions of the zonal offices
1. Approving grants for the manufacture, and import of new drugs/medicinal products including vaccines, etc.	1. Regular inspection of the premises of drug manufacturers
2. Grants licences to import drugs	2. Inspection of manufacturers for WHO good manufacturing practices (GMP)
3. Approves grants for conducting clinical trials	3. Inspection of private testing laboratories
4. Functions as Central License Approving Authority (CLAA) for running blood banks, manufacturing diagnostic kits, etc.	4. Inspection for capacity assessment as required by the central agency
5. Registering foreign manufacturers	5. Inspections in response to complaints
6. Grants permission to manufacture drugs exclusively for export	6. Investigating the 'Low drug standards'
7. Constitute meetings of Drugs Technical Advisory Board (DTAB) Drugs Consultative Committee (DCC) to scrutinize the functioning of the DCA and suggest amendments if necessary, and to maintain uniformity	7. Launching legal actions in discrepancies
8. Co-ordinating with the state drug authorities to maintain uniformity	8. Grant no objection certificate (NOC) to manufacturer for examination, test, and analysis
9. Monitors ADR's (pharmacovigilance)	9. Grant NOC to manufacture drugs exclusively for export purposes
10. Enforcing Section 26A of the Drugs and Cosmetics Act to ban harmful drugs	10. Grant permission to import drugs for personal use
11. Inspection of clinical trial sites	11. Grant NOC to import dual use material not for medical use
12. Conducting training and workshops to improve quality control	12. Test and analyse drugs and cosmetics

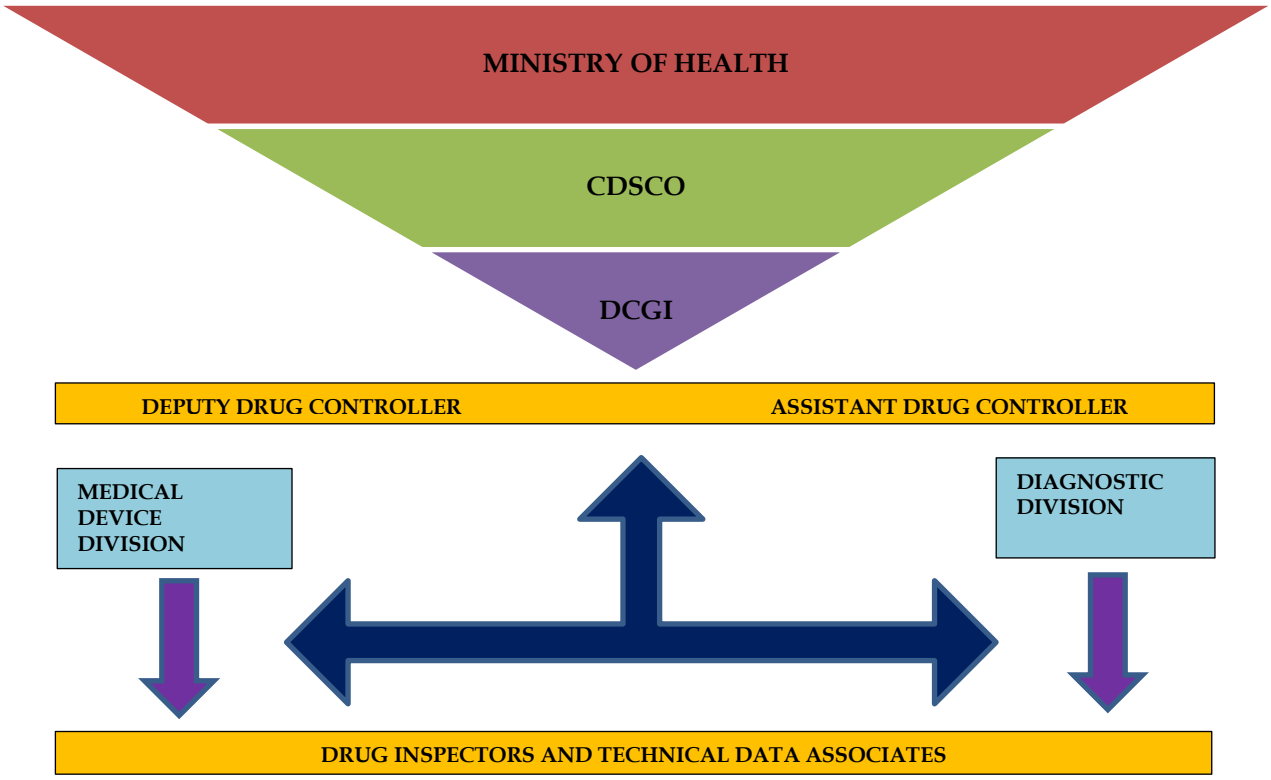

Figure 3. The organizational structure of Indian pharmaceutical regulation

The regulatory authority in India for pharmaceutical products functions under the CDSCO, which is plagued by structural challenges related to harmonizing its activities in coordination with the individual states' drug regulatory authorities (SDRA's)[47]. The organizational structure of the Indian pharmaceutical regulatory authorities depicted in **Figure 3**[48]. The Indian regulatory authority for drugs constitutes seven main bodies that include the CDSCO, National Institute of Health & Family Welfare (NIHFW), ICMR, Drug Technical Advisory Board (DTAB), Central Drug Testing Laboratory (CDTL), Indian Pharmacopoeia Commission (IPC), and the National Pharmaceutical Pricing Authority (NPPA)[48].

THE PHARMACOVIGILANCE LAWS AND GUIDELINES

Pharmacovigilance is a process of assessing a drug's safety, and such a process will ensure that the drugs do not harm but benefit. The process of Pharmacovigilance is a lengthy one that involves four crucial phases that includes the collection of data, collation of data, analysis of data, and communication[49]. Regulatory agencies like the US FDA perform Pharmacovigilance. The FDA regulates all the issues related to drugs, food, cosmetics, biologics, and medical devices. FDA does not regulate advertising (except drugs, medical devices, and tobacco), alcoholic beverages, meat, poultry, illicit drug abuse, and health insurance. In the EU, all matters related to the regulation of medicinal products come under the EU legislation (EudraLex), European Directorate for the Quality of Medicines and Healthcare (EDQM), European Medicines Agency (EMEA), and Heads of Medicines Agencies (HMA). Created in 1996, the EDQM harmonizes the regulatory activities across the EU and ensures the quality and safety of pharmaceutical products[50]. In Japan, pharmaceutical affairs are regulated by the pharmaceutical affairs law (2005), the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), and the National Institute of Infectious Diseases (NIID)[51].

It was important to have a harmonized approach because the regulatory agencies have different rules and regulations in the respective countries. This was brought about by the International Conference on Harmonization (ICH) of clinical research that proposes technical requirements for registering pharmaceutical products for human use[52]. ICH was first convened in 1990, when the US, EU, and Japanese regulatory policies were harmonized since drug development was a global scenario. The structure and organization of ICH consisted of six major sponsors/parties and three official observers, as shown in **Table IX**.

Table IX. The structure and organization of ICH

ICH-six official partners	ICH-observers
EU: European Commission + EMA and CHMP	World Health Organisation (WHO)
EFPIA (European Federation of Pharmaceutical Industries & Associations)	European Free Trade Area (EFTA)
Japan: MHLW (Ministry of Health and Welfare)	Canada (Health Protection Branch)
JPMA (Japanese Pharmaceutical Manuf. Association)	Interested Parties
US: FDA (US Food and Drug Administration)	
PhRMA (Pharmaceutical Research and Manufacturers of America)	

Pharmacovigilance deals with the assessment of risks associated with pharmaceutical products. It deals with the activities that find, evaluate, understand, and prevent adverse drug reactions (ADR) and other unwarranted drug-related consequences. In India, pharmacovigilance activities date back to 1986, when for the first time, an adverse drug reaction monitoring system was proposed in India. India started participating in the WHO-ADR in 1998, and in 2004, it started a national pharmacovigilance program (PvPI). The ADR reporting system in India follows reports of ADR by healthcare workers, consumer reporting, and public health programs (PHP). It is regulated by the CDSCO, the ministry, and the India pharmacopeia commission headquartered in Ghaziabad, the national coordinating center (NCC)[53]. India, the third-highest active pharmaceutical ingredient (API) producing/testing country in the world, requires a robust system of ADR reporting, as noted by recent research[54].

RISK MANAGEMENT AND SPONTANEOUS REPORTING IN CLINICAL RESEARCH

The most significant aspect of a clinical trial/research is data collection. Because there is a tremendous amount of patient/participant data that needs to be collected and because there are many medical terminologies, we need a harmonized approach[55]. We have what is called MedDRA or Medical Dictionary to solve this issue. MedDRA includes a clinically validated international medical terminology dictionary, which can be used by the regulatory authorities and the pharmaceutical industry during various clinical trial processes that include pre- and post-marketing activities, data entry, retrieval, evaluation, and presentation. MedDRA is now available in English, Japanese, Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese, and Spanish[56]. ICH also recommends an adverse event classification dictionary which can be used for reposting the adverse events through human phases of the clinical trial. The MedDRA (Version 19.0, March 2016, latest version) consists of internationally accepted medical terminology derived from various sources like the WHO-ART, COSTART, HARTS, ICD-9, and ICD 9-CM, which saves time, resources, and money. It is managed by the Maintenance and Support Services Organization (MSSO). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) is the trustee, and the ICH steering committee holds the intellectual property rights of MedDRA. MedDRA aims to provide a standard and uniform platform for communication between regulatory agencies and the pharmaceutical industry. MedDRA encourages online/electronic submissions for applications related to various phases of clinical research. MedDRA database includes disease, diagnosis, signs and symptoms, therapeutic interventions, diagnostic tests and their qualitative results, medical and surgical procedures, and medical and social history. The terms related to the patient demographic characteristics, drug product device failure, and clinical trial/study design are not included in MedDRA[57]. The MedDRA is organized into five levels; the System Organ Class (SOC) forms the first level, which has 26 terms that include Card-Cardiac disorder, Cong-Congenital, familial, and genetic disorders, Endo-Endocrine disorders, Gastr-Gastrointestinal Disorders, Genrl-General disorders, and administration site conditions, Inj & P-Injury, poisoning, and procedural complications, Preg-Pregnancy, puerperium, and perinatal conditions. Levels 2-4, respectively, are High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT), and finally into, Lowest Level Terms (LLT) forming. MedDRA also includes Standardized MedDRA Queries (SMQs), which define a medical condition within an area of interest[58].

Spontaneous reporting is an observation by the clinician/physician during their patient management procedure related to the activity of a drug. Because of their nature of spontaneity, such reports face criticism and demand confirmation before being accepted by healthcare practitioners[59]. Medical practitioners contribute to spontaneous reporting because they are motivated to advance clinical knowledge/understanding, a previously unknown reaction, the reaction in response to a novel drug, drug, and reaction associations, and the severity of ADR[60]. Spontaneous reporting of ADRs is intended to

convey an important message to the medical practitioners who prescribe the drugs, to understand the epidemiological implications, and as a part of continuing medical education[61].

RESEARCH WRITING, COMMUNICATION, AND THE ROLES OF STAKEHOLDERS

Research is considered complete only if its results have been discussed as a scientific publication. It is the responsibility of researchers and publishing editors/publishers to carefully evaluate the results submitted by the authors and publish both positive and negative results, which will improve patient care. There is an increased gap between the research activities, their results, and clinical practice. Wherever necessary, the research results must be made available to the policymakers and all the stakeholders (patients, others), allowing discussions to make public health-related policy decisions[62]. Scientific publications are generally done in journals, which are peer-reviewed before being published. The journals are indexed/archived in various databases, protecting the content permanently. The major indexing agencies for medical journals include Index Medicus, PubMed, Scopus, Web of Science, and others[63].

Different research publications include evidence-based reviews (systematic reviews/Cochrane reviews). Such publications evaluate the available research studies and present the results in a manner that healthcare practitioners can easily understand. It helps in developing detailed knowledge which can be translated into practice. Although scientific publications in journals are intended for the scientific community, there are several other communications which are needed to be done. Other communications include communications to the funding agencies, health professionals, policymakers, patients, the community, the public, and the media[64]. A scientific publication is a clear and honestly written research work intended for the public's benefit. An original research work (observational/experimental) is usually divided into an Abstract/summary, Keywords, Introduction, Methods, Results, and Discussion. To have uniformity in scientific communications, the International Committee of Medical Journal Editors (ICMJE) recommends that biomedical journals follow specific guidelines for considering the publication of scientific papers in journals[65]. A few recommendations of ICMJE are listed in **Table X**.

The manuscript may contain acknowledgments, financial declarations, and conflicts of interest at the end of the entire manuscript before the references. Finally, the manuscript lists cited references that follow a uniform pattern, like the Vancouver and Harvard styles[66]. Research communications assume increased importance when the results are communicated/presented to the stakeholders, who may be interested in/affected by the research results/conclusions. It is often crucial that the research results are considered a cornerstone for making policy decisions, especially concerning protecting the environment and public health[67]. Interaction between researchers and the stakeholders is essential for improved communication of the research results. There is a responsibility on the part of both the researchers and the scientists for their responsibility towards society[68]. Stakeholders are all those individuals and institutions that may be affected by the research outcome. A strong relationship and understanding between the stakeholders and the researchers are essential for research success[69].

Table X. The recommendations of ICMJE with respect to scientific publications

Section of the scientific communication	Recommended guideline
Title	Must convey the zest of the paper in as few words as possible, no abbreviations, ideally restricted to 10-12 words and 30-50 characters
Abstract	Convey the message of the full paper, may be structured or unstructured, limited to 250 characters, written in past tense describing in brief about the work, no references
Keywords	Facilitates indexing, and retrieval, must have a minimum of three, and may be up to 10, chosen from within the abstract, no abbreviations, preferably listed in the medical subject heading (MeSH) as listed in PubMed
Introduction	The perspective of the chosen work, background, and why did the authors choose to work on it? Can have limited references
Methods	What has been done? clear methodology including the ethical concerns, statistical applications, can have references
Results	What has been found out? Clearly presented in Tables, Figures, Graphs, etc., no references
Discussion	Results are analysed and discussed, generally in comparison to available literature, mention the limitations of study with future perspectives, and well referenced
Conclusions	Should be a minimum of two sentences, drawn from the results of the study, abstain from claims not drawn from the results

PATENTING, PUBLICATION, ASSESSMENT, AND EVALUATION OF RESEARCH

Among the various essential aspects of clinical research/trials, the publication of the research results assumes increased significance. Also, the sponsor may proceed with the patent application with the help of the data generated from a clinical trial. Other significant issues include ethical concerns, conflict of interest (COI), and copyright-related aspects. The sponsors may influence the research publications drawn from a clinical trial, and only favorable results may be published by not revealing the study's negative results. Also, authorship problems could arise when a ghostwriter is chosen to write the manuscript and the authorship criteria do not follow the ICMJE recommendations[1]. Research publications also involve copyright issues, where the authors of previous research must be given due credit. All material should be cited only after acquiring the permission of the concerned parties. Journal publications can also be plagued by the issue of plagiarism and duplicate/redundant publications. The copy of an idea, words, and any other material from previously published content without citation and not giving due credit to the copyright holder is termed plagiarism. Protection of patient privacy is another critical aspect of journal publication, where the study's participants and their identities should not be revealed[70].
Scientific fraud may also arise because of improper study design, bias, inappropriate statistical methods to draw conclusions, fabrication, cooking up the data, and undue data trimming. The Committee on Publication Ethics (COPE) was constituted in the year 1997 in the United Kingdom to control unethical practices in the research and publication processes. The COPE vests the responsibility of the published content on the editors, and it was recommended that the journals retract the fraudulent papers after a thorough inquiry[71]. Assessment and evaluation of research is the most crucial step in a journal publication process. Mostly it is done through the peer-reviewing process. For the research to be useful/fruitful, the research results must be applied by patenting and manufacturing. Patents are legal documents that entitle the inventor with the rights to novel technical innovations/ideas[72]. Published research requires evaluation by peers in the respective field. More so, the parameter that is taken as the criteria for assessing the published article is its citations[73]. The number of times the published content has been cited by another researcher in their research publication reveals the citation's impact on the article/publication. Patents are also an indicator that determines the potential of the research in the industry[74]. In recent research from Germany, the main motive was to produce a publication, and in most instances, a patent has a commercial motive[75].

THE CURRENT PERSPECTIVES

The clinical research process requires certain concepts that include the identification of a research problem. A thorough literature review is performed, and a conceptual framework is developed. Later experts in the related field are approached for collaboration and conduction of clinical trials. Another significant aspect of clinical research is identifying the population's opinion. Constructing a theoretical design is essential while conducting clinical research, achieved only through an extensive literature survey and expert collaboration. The pictorial representation of the clinical research type is shown in **Figure 4**[76].
Recent research has stressed the importance of establishing state-of-the-art research and development facilities in India. It also signifies the necessity for Indian pharmaceutical manufacturing companies to adhere to international (US and EU) regulatory requirements. Such practices by the Indian pharmaceutics firm may encourage the production of generic drugs and enhance drug exports to foreign countries. This study also observed that the expenditure on pharmaceutical R&D by Indian manufacturers had significantly increased in the last decade-and-a-half, and India contributed to 40% of the world's Abbreviated New Drug Applications (ANDA)[77]. Recently, the Association of Southeast Nations (ASEAN) was formed as a regional organization that could become a platform for Southeast Asian countries to harmonize drug regulatory requirements. There are currently ten countries, including the major country Singapore, Malaysia, Thailand, Indonesia, Philippines, Brunei Darussalam, Laos, Myanmar, Vietnam, and Cambodia, unfortunately without India[78].
Approval of novel drugs is essential to functioning regulatory authorities like the US FDA. Novel and repurposed drugs are significantly essential concerning improved patient care. A recent study assessed the trends in approving new drugs by the US FDA in the last decade (2000-2017). It was observed that the FDA's Centre for Drug Evaluation and Research (CDER), which summarizes novel drugs, is instrumental in advancing clinical research and improving clinical care. It was noted that there was an increased approval rate for new drugs against cancer and related biologics and relatively slow progress for the approval of neurological drugs (antipsychotic, anti-depression) and lifestyle diseases (obesity, diabetes, and others)[79]. There

is no doubt about the contribution of clinical research to the advancement of healthcare, as evidenced by the reduction in the morbidity and mortality associated with several illnesses that include both contagious and non-contagious diseases. Vaccines against polio and many treatments for cardiovascular diseases are a couple of examples that signify the importance of clinical research[80]. The regulatory requirements for manufacturing pharmaceutical products vary between different countries. But the prominent function/role played by the regulatory bodies is to supervise the manufacture, distribution, and promotion and ensure that the medicinal products are safe and have quality and efficacy[81].

The efficiency of the regulatory bodies is instrumental in developing quality generic medicines. Generic drugs are remarkably like the innovator product (patented) and show an equal bioequivalence value as an innovator drug in terms of quality, safety, and efficiency[82]. The prevalent inconsistencies among various regulatory authorities worldwide have been highlighted by the perception/categorization of herbal medicine (HM) compared to five countries. This study noted that HM had a different definition and was under a different law, requirement, restriction, and preparation type. Except for the US, which considered HM a food supplement/herb that does not require prior permission before marketing, other countries, including the UK, Germany, United Arab Emirates (UAE), and Bahrain, offered simple regulatory requirements[83].

Good knowledge of the standards and procedures followed by national and international regulatory agencies could improve the standards of pharmaceutical manufacturing companies. It must be noted that the US FDA approves generic drugs following the same stringent regulatory approval procedures, and therefore the quality of the generic drugs will be very similar to that of an innovative/patented drug[84]. It has recently been emphasized that pharmacovigilance assumes increased significance in the era of 'Big data' where a large amount of clinical research data is generated. The post-marketing stage has been noted to have a significant role in pharmacovigilance, and it is instrumental in identifying additional safety issues with the drugs[85].

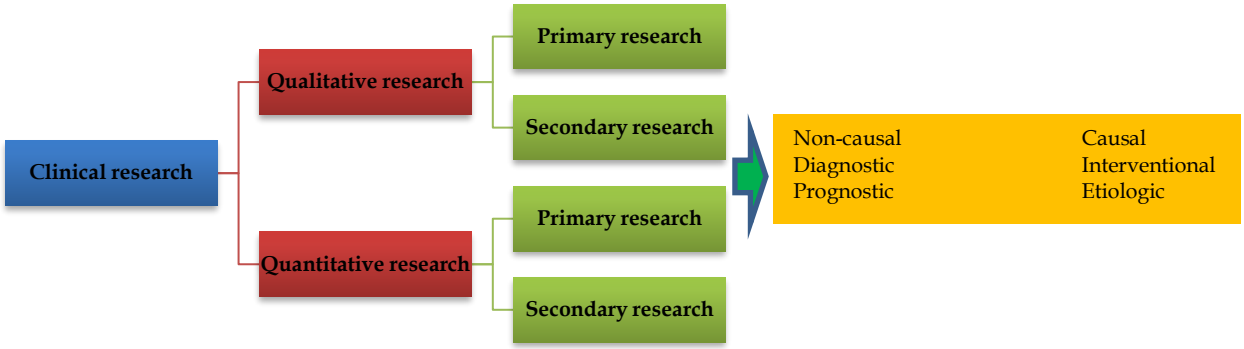

Figure 4. The pictorial representation of the types of clinical research

CONCLUSION

Clinical trials and research related to developing, manufacturing, and marketing novel pharmaceutical drugs and devices have been instrumental in resolving many public health-related problems. However, this process is highly critical due to the national and international regulatory requirements. Also, because clinical research involves human participants, the role played by the regulatory authorities, pharmacovigilance laws, and risk assessment assumes increased significance. The patents obtained and the research publications consequent to the clinical research/trials are equally crucial for the pharmaceutical drug and devices to enter the markets and be available in the public domain for use among humans.

ACKNOWLEDGMENT

The authors thank our respective Institutions and Universities. This study did not receive any funding.

AUTHORS' CONTRIBUTION

Venkataramana Kandi: conceptualized, prepared the initial draft, revised, and edited the manuscript. **Sabitha Vadakedath**, **Purna Singh Addanki**, **Vikram Godishala**, and **Venkata Bharatkumar Pinnelli**: performed revisions. All the authors approved the final draft.

DATA AVAILABILITY

Not applicable.

CONFLICT OF INTEREST

None.

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