

Ethical Considerations in Clinical Research: A Comprehensive Review

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Abstract Clinical studies involve research that is carried out in human beings and has direct implications on the health of people who participate in it as study subjects. Moreover, clinical trials are performed on healthy and diseased human subjects, wherein the safety and efficacy of a novel drug/device are tested. Therefore, the study design and the subject recruitment assumes increased significance. In this review we attempt to comprehensively discuss the importance of ethics in clinical research and specific ethical considerations concerning the evaluation of medical products, epidemiological studies, human genetics, and genomic research, transplantation studies, reproductive procedures/interventions, research among geriatric and pediatric populations and research involving the development of vaccines and diagnostic devices.

Keywords: *clinical studies, clinical research, human subjects, ethics, ethical considerations, vaccines, devices, medical products*

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1. Introduction

The term clinical research does not necessarily mean research that is conducted concerning a new drug/clinical entity. It refers to all the types of research that include the recruitment of human participants. Clinical research covers all the areas but is not limited to treatment and diagnosis. Areas concerning public health, like the prevention of diseases with vaccines, epidemiological research, and the research that analyses the patient records, research on stored biological specimens also falls under the preview of clinical research. The clinical research, under its umbrella, ensures that the research is carried out following the principles and the guidelines formulated both by the local, national, and international bodies like the Institutional Ethics Committee (IEC), and the International Council for Harmonization (ICH). Because clinical research is carried out in human beings, ethical considerations like the protection of the rights, safety, well-being, autonomy, right to compensation of the study participants assume increased significance [1]. It has been reported that the IEC, during its review process seriously considers three issues about the conduction of clinical trial research, which include science, ethics, and data quality. Such a review would ensure that research has been initiated to improve the current knowledge and ensure benefits to the people and doesn't cause unnecessary harm to the study participants [2].

To conduct clinical research involving an investigational new product/drug, the sponsors/ investigators must justify the research and determine the objectives. The study must take into consideration all the ethical guidelines laid out by both the local and the international regulatory agencies. The sponsor and the investigators must take responsibility for the rights of the participants. Also, they must ensure that device principles to recruit the participants, the exclusion criteria, and the terms of voluntary participation and withdrawal of the subjects any time during the study, obtaining well-informed consent. The investigational new drug (IND) must be carefully handled and stored by the principles laid down by the investigational brochure. The IND must be adequately evaluated for its similarity to an already available drug, the relevant pre-clinical data that supports the aims and objectives of the study. A well-structured protocol paves way for successful clinical research. The essential elements of a protocol include the title, date, identification number, any amendments which are again numbered, name, address, contact numbers of the sponsors, and the monitor or a clinical research organizer (CRO).

The protocol must also contain the name, title, and contact numbers of the medical experts designated by the sponsor, the investigators who conduct the study, the names address, and the contact numbers of the centers of the study. The protocol should have information regarding the potential foreseeable risks and the benefits to studying participants. It must contain information about the type of the study design that includes if the study is randomized,

comparative, blinded/open, placebo-controlled, parallel groups, cross-over technique, double-blind, single-blind, randomization, and placebo-controlled. Before the initiation of the drug, the trial protocol must have passed the review of the IEC. The IEC must review, the recruitment procedures followed concerning special/vulnerable group subjects like the people belonging to the economically weak communities.

The responsibility of the sponsors to ensure the quality controls, quality assurance, and publication and reporting policies assume increased significance. The protocol must mention that the data generated from the study will be presented for monitoring, audits, review by the independent ethics committee, and other regulatory inspections. The IEC must ensure that each protocol must be submitted along with a copy of a case report form (CRF), and a well-drafted informed consent form. The protocol must mention in detail the financial agreements (if any) between the sponsor-researcher, sponsor-manufacturer, and any other relationship. It also should mention the compensation and the accident/injury monitoring/handling policy. The clinical research sponsors and the investigators must ensure that the study is conducted following the ethical (Declaration of Helsinki/ Ethical Guidelines for Biomedical Research on Human Subjects by ICMR) and safety considerations of the participants. The sponsor must make a legal agreement/contract both with the investigator and the institution. The sponsor should provide the protocol, the standard operating procedures (SOP), and the investigational brochure for review and evaluation before the start of the study. It is the responsibility of the sponsor to ensure that the study is conducted as per good clinical practice (GCP) guidelines.

Clinical research is carried out not only by the pharmaceutical industries, which is usually on a large scale but also is done by the clinicians, academicians at various institutions that include the medical college, hospitals, and small-time research centers. Research by a pharmaceutical company involves huge financial commitments, whereas research carried out by the academicians/clinicians as a part of his/her teaching/physicians' role usually involves less/no financial obligations. The industry people may follow several regulations, which may not be the case by the academicians/clinicians. Therefore, such research and its investigators are required to understand the various aspects of clinical research including the principles, and guidelines of conducting the research. They must satisfy the regulations recommended by the CDSCO, Drugs and Cosmetics Act (1940) and Drugs and Cosmetics Rules (1945), ethical guidelines of the Indian Council of Medical Research (2006), and the Indian Good Clinical Practice Guideline (2001) [19].

In the current review, we comprehensively discuss the general ethical considerations involved in clinical research and specific ethical issues concerning the reviews of study/protocol, evaluation of medical products, epidemiological studies, human genetics, and genomic research, transplantation studies, reproductive procedures/interventions, research among geriatric and pediatric populations and research involving vaccines and diagnostic devices.

2. General Ethical Issues and Review Procedures in Clinical Research

It is essential to understand the general ethical issues and the review process involved before conducting the clinical research. Since clinical research requires the participation of humans in the form of study subjects, individuals are recruited based on certain criteria and principles designated by the regulatory bodies in the form of informed consent. Among the basic principles which should be considered before enrolling the study participants, the respect for autonomy (participant must be allowed to decide by himself both participate and to stop participating if he/she wishes), beneficence (participant must get the benefit and should never be harmed), non-maleficence (participants must be made completely aware of the study process), and justice (participants must be given the best deal irrespective of the study results). The study participants should be made aware of all the information regarding the duration, procedures followed, investigations to be conducted, potential risks including the foreseeable and those which may be unknown, benefits of the study both to the participants and to the society/community, compensation details, risk management procedures including the treatments available, confidentiality issues, losses (no loss of benefits if the participant withdraws) and benefits concerning commercialization.

The informed consent and its contents are thoroughly evaluated by the respective institutional review boards (IRB's)/IEC/research ethics board (REB) before the approval of the clinical research protocol. The basic responsibilities of the review boards are to ensure the participant's rights, dignity, and well-being. The clinical research is conducted in a single center, or it may be a multi-center study. Also, the participants may belong to different communities and have varied cultural and societal backgrounds. Therefore, the information regarding the research to be conducted must be provided to the participants in a manner that is suitable for them to completely understand. It is important to acquire a signed informed consent wherever possible (verbal consent recorded in a video in some cases) and if a participant is uneducated, a thumb impression may be taken.

Waiver of informed consent may be considered in cases where the participants may be taking part in a Human immunodeficiency virus (HIV) study and are HIV positive, where it is difficult to keep the confidentiality. Also, informed consent may be waived off during an emergency, where the patients are treated with a novel drug considering the risks to benefit ratio. The participants must be given the liberty to ask any relevant questions regarding the clinical research process and the investigators must take fresh informed consent during any deviations from the study process. Depending on the nature of a study, the review boards must screen and categorize the protocols submitted for approval into three categories. The review boards, considering the type of the study and the associated risks to the participant's group the protocols are categorized into a) exempted from review, b) expedited review, and c) full review. The ideal composition of an institutional review board and the study

categorization based on risk to the participants is shown in [Table 1](#) and [Table 2](#) respectively.

Table 1. Composition of an ideal institutional review board

S.No.	Role	Position
1	Chairman	From the other organization
2	Member secretary	Basic scientist/clinician
3	Member	Pharmacist
4	Member	Basic scientist/clinician
5	Member	Basic scientist/clinician
6	Member	Basic scientist/clinician
7	Member	Social worker
8	Member	Legal expert

Table 2. The categorization of review of protocols based on the type of study

S.No.	Type of Review	Risk to participants	Type of study	Exemptions
1	Exempted from review	No risk	Research on educational practices, research on teaching strategies, research on the comparison of instructional methods, research on curriculum, and classroom management techniques	Research on educational tests, surveys/interviews which recruit and identify the participants,
2	Expedited review	Minimal risk	Research on patient data, records, and specimen collected for clinical purpose. Research with approved drugs Research during outbreaks, disasters, and emergency situations	Study on drug interactions and study including vulnerable population Minor adverse events (AE)/adverse drug reactions are reported
3	Full review	More than minimal risk	All the studies which do not qualify either for exempted or expedited review All the studies that involve collection of blood and other specimens like the finger prick, ear prick, skin scrapings, etc. Patients undergoing surgeries, and diagnostic procedures like the magnetic resonance imaging (MRI), compute tomography (CT) scans, and others	None

3. Ethical Considerations for Clinical Evaluation of Medical Products

This concept elaborates on the principles and guidelines of clinical evaluation of drugs that include the different phases of a clinical trial, the specific principles of drug trials, surgical procedures, device trials, vaccine trials, trials involving herbal medicine, and methods of monitoring and reporting adverse drug reactions. It has been noted that the complexities associated with human clinical research have increased over time. The most basic principles involved in the conduction of human clinical research are autonomy, non-maleficence, beneficence, and justice. A clinical trial (randomized, single/double-blinded), according to the revised schedule "Y" of the drugs and cosmetic act (DCA) 2005 is defined as the systematic study of a new medical product (drug/device/surgical procedure/diagnostic test/vaccine/herbal medicine), to assess its clinical and pharmacological (pharmacokinetics and pharmacodynamics) effects, safety (adverse reactions/events), and efficacy.

According to the DCA-1945, a drug to be tested is called a new chemical entity (NCE), which may be an approved drug being tested for a different indication, at a different dosage, and in a different route of administration. It may also include the study of two individually approved drugs in combination (interaction studies), called fixed

drug combinations (FDC). The medical product trials involve several sensitive issues that include the use of a placebo (a dummy), and a sham surgery, which by any means do not satisfy the basic principles of clinical research involving humans as suggested by the Helsinki declaration. Drug trials which include the medical products not approved by the regulatory authorities come under the preview of the law of the land.

The guidelines and the general principles while designing, conducting, recording, and reporting clinical research may be suggested by the local regulatory authorities like the Indian Good Clinical Practices (GCP) of India, which follow the regulatory guidelines recommended by the international authorities like the World Health Organization (WHO) and International Committee on Harmonization (ICH). A clinical trial is conducted to study an NCE, comparison of two approved drugs, and the efficacy and the effects of combination drugs. A clinical trial involves four phases that include phases I, II, III, and IV. Also, the clinical research involves special studies called bioavailability/bioequivalence studies (testing new drug dosage forms and the drugs approved in other countries for systemic absorption) and the dissolution studies (testing the solid dosage forms of drugs, their dosage, and bioavailability in different formulations). The phases of clinical trials, their roles, and the nature of studies are elaborated in [Table 3](#).

Table 3. Different phases of clinical trial studies

S. No.	Phase of clinical trial	Type of study	Nature of study
1	Phase I	Non-therapeutic trial	Around 20-50 healthy subjects are recruited. Establishes safe dose range, the maximum tolerated dose and examines the pharmacokinetic and pharmacodynamic effects Single center studies
2	Phase II	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. Multicenter studies
3	Phase III	Therapeutic confirmatory trial	More than 300 patients of either sex are recruited in this study. Examines the efficacy and the safety of the drug Comparison of test drug with the placebo/standard drug Adverse drug reactions/adverse events
4	Phase IV	Post-approval study	After approval/post-licensure and post-marketing studies. Following up of the patients for a very long time for potential adverse reactions and drug-drug interactions

Table 4. classification of the medical devices into four classes based on their risk levels

CATEGORY	TYPE OF RISK	DEVICES
A	Low risk	Thermometer, blood pressure apparatus, tongue depressor
B	Low to moderate risk	Hypodermic needles
C	Moderate to high risk	Bone fixing/supporting plates, ventilators
D	High risk	Implants like the heart valves, pacemakers, defibrillators

The ICMR had revised the regulations about the ethical considerations in research involving human participants. This guideline, which was released in 2017, was the 4th amendment to the research guidelines involving human subjects in India [3]. This release had revised the principles regarding the issues about the general ethical issues, ethics review procedures, research in a vulnerable population, principles concerning clinical trials of drugs, interventions, public health research, social, behavioral sciences research, research during emergencies, disasters/calamities, and storage of biological materials, bio-banking, and data handling. In the united states of America (USA), the food and drugs administration's (FDA) Food, Drug, and Cosmetic Act frames the investigational device exemption (IDE) rules which govern the safety, efficacy, and performance of a medical device [4]. In India, the regulatory guidelines with regards to medical devices do not fall under the drugs and cosmetics act (DCA) which deals with drugs. The M-III schedule under the new central drug standards control organization (CDSO) guidelines classify the medical devices into four classes (A, B, C, and D) based on their risk levels to patients as shown in Table 4 [5].

4. Ethical Considerations for Epidemiological Studies

Clinical research involves studies that are undertaken to identify public health problems. Such research which is undertaken at the community level including a large group of the population comes under the category of cross-sectional, case-control, cohort, and observational studies. In countries like India and other developing countries, epidemiological studies on both communicable (infectious diseases) and non-communicable (heart, liver, and lung diseases) diseases assume increased significance. Such epidemiological studies, which include both the healthy as well as diseased people help in identifying the causes/risk factors and developing mechanisms to prevent them in the future. Epidemiological research may be carried out in the form of research, a health program, or a surveillance activity.

Ethical concerns in epidemiological studies are multifaceted and complex majorly because of the length of the duration of the study, the number, and the versatility of the participants who belong to the different socio-economic milieu. Epidemiological studies are different types of clinical research, and they assume significance because of their association with a huge financial commitment. Therefore, extreme care is required to address all the concerns including the practical aspects, the technical areas, and the ethical concerns before initiating the study. Different types of epidemiological studies and their applications are elaborated in Table 5.

Table 5. Different types of epidemiological studies and their applications

S.No.	Epidemiological study type	Applications	Consent
1	Observational study	Uses a predefined parameter, a group of predefined people, limited time, and assesses the exposure to risks affecting the health.	Required
2	Cross-sectional study/survey	Almost includes the entire population/random sample representative group. Uses questionnaire to collect the data in single contact. Tries to find the cause of a disease or the potential risk factors.	Required
3	Case-control study	Assesses the history of exposure to risks in cases and compares them with the healthy controls with similar risk exposures, age, sex, and other sociodemographic characters.	Required unless the study is done by using the past records
4	Cohort study (longitudinal/prospective)	Groups of individuals with different exposure levels to potential risk factors. Participants are observed over a long time (months-years). Rates of disease/condition with respect to the exposure to risk factors is calculated	Required
5	Experimental study	Alter exposures to risk among the study groups to examine the effects. Involves interventions and are usually randomized.	Required

The epidemiological research follows the guidelines recommended by the council of an international organization on medical sciences (CIOMS) and the WHO. The ethical guidelines majorly satisfy the safety concerns of the study population and make sure that no harm is done to the participants, maximize benefits to both the individuals and the community involved, maintenance of scientific objectivity, and integrity of the study results. In cohort and experimental studies, the group with the potential risk factors is observed and intervention is blinded with placebo respectively, which poses a serious ethical concern. This may pose risk to a certain group of study participants which needs to be ethically justified. Involving the participants, their community leaders, village heads, and the panchayat leaders may be crucial in protecting the participant's rights against financial inducements, privacy, and confidentiality issues.

The epidemiological studies majorly include the public health programs and research activities are undertaken by the governments. Such research usually involves a large group of population and involves huge finances. Therefore, addressing the ethical issues before the initiation of the epidemiological studies could be instrumental in the success of the programs/research activities [6]. Epidemiological studies like health systems research (HSR) are a unique type of clinical research since it doesn't involve the trial of drugs. A previous study highlights the significance of eight ethical issues that may determine the study in terms of the protection of the human rights of the study participants. These issues include the nature of the intervention, types of research subjects, units of intervention and observation, informed consent, controls and comparisons, risk assessment, the inclusion of vulnerable groups, and benefits of research [7]. The principles concerning the ethics concerning the conduction and analysis of epidemiological research were initially proposed by the Council for International Organizations of Medical Sciences (CIOMS) in the year 1991. Although the same ethical guidelines were suggested for the epidemiological studies, later it was realized that such research is different from normal research, and it needs some special considerations. Given the implications of the epidemiological research both on the individuals as well as the community, certain principles were suggested that included minimizing risk on the patients and benefiting both the participants and the community. It emphasizes maintaining public trust in research results and adopting high scientific standards and incorporating representatives from the community into the team. Also, it elaborates principles of adhering to the community commitments, to ensure that the benefits are extended to the community, besides keeping respect for cultural diversities [8].

5. Ethical Considerations for Human Genetics and Genomic Research

The clinical research involving the human genome is associated with the risks and benefits, confidentiality issues, parental, newborn, children, and anonymous testing for genetic disorders. After the completion of human genome sequencing for the first time in the year

2000, scientists acquired an improved understanding of the cause of many diseases. This has paved the way for the development of regulations that govern researchers/scientists who carry out genetic mapping and genetic diagnoses. With increased knowledge of human genetics, scientists have been trying to cure and prevent genetic diseases using gene therapy (somatic cell gene therapy, germline therapy). This had prompted ethical concerns throughout the world, and the regulatory authorities make sure that such a therapeutic approach should not be misused and must be available to all mankind irrespective of their financial status.

Several gene banks and cell-line repositories have started to function by collecting the human genome/DNA/tissue/ cord blood for future use. The collections can be of two types: the unidentified samples, and the identified samples/collections. The samples may also be collected exclusively for research and are labeled as anonymous samples, unlinked samples, and coded samples. The genetic research also follows the same ethical guidelines as do the other types of clinical research, where protecting the participant's rights is given increased priority. Also, genetic research is concerned not only with the individuals but also with the family and the community/society. Therefore, additional care is taken to address ethical concerns to avoid physical, psychological harm, and damage to familial relationships.

Clinical research concerning genetics appears to be quite tricky as it may lead to several unforeseen consequences that may reflect on individuals, families, and society. Genetic counseling of the participants/families requires that they share a lot of the personal information with the investigators rising potential ethical concerns like undue inducements (financial). Confidentiality appears to be at stake during and after the genetic counseling and potential diagnosis. Therefore, it is important to de-link the research results and consider revealing the results of informed consent in cases where the results are beneficial both to the individuals and the community.

Genetic research requires certain special considerations while obtaining informed consent from the participants of the study. Because of the potential implications associated with the diagnosis of genetic diseases, informed consent is obtained in-group from all the representatives of the community which may be led by a group/community head/leader/representative. The informed consent should contain necessary relevant information of the research process, must carry information about the potential risks, and must give the time and choice of either participating/not/withdrawing from the study. After the discovery of the double-helical structure of the deoxyribonucleic acid (DNA), and the human genome project, the research concerning human genetics started evolving. The genomic research deals with the identification of the genes coding for various proteins, and enzymes, knowing the mutations that may cause drug resistance, and cancers, and finding out the genetic basis of disease/infection susceptibility among different people. Because of the financial consideration and the possibility of personalized medicine taking a toll on the ethical aspects in genetics research that can be protected by well-informed consent, and a thorough ethics review [9]. The emergence of newer microbial infections had thrown

several public health challenges both to the governments and the healthcare workers. In recent research, a newer technology named Gene drive technology was proposed as a potentially beneficial and cost-effective strategy for controlling the transmission of deadly and debilitating microbial infections in people worldwide. The gene drive technology facilitates the inheritance of the gene of interest, thereby increasing its prevalence in the community [10].

6. Ethical Considerations for Transplantation Research

Transplantation is a process where an organ from one individual (donor) is grafted into a different individual (recipient). Transplantations are a complex surgical procedure that poses a potential ethical concern. The subject of transplantation is emerging in the twenty-first century, and although we stand in its infancy, the subject is ever-growing. There are different types of transplantation procedures that include live donor transplants, cadaver transplants (cadaver donor), the xeno-transplantation (donors are animals other than humans, usually homo-sapiens, chimpanzees), and the transplantation carried out for cosmetic purposes. Cadaveric transplantation poses an ethical concern because here the donor is dead.

The donor's death must be scientifically proven to perform a transplantation procedure. According to the 'Transplantation of Human Organs Act, 1994' with 'Transplantation of Human Organs Rules, 1995, death may be an irreversible loss of the function of the brainstem and loss of brain-stem reflexes (no pupil constriction to light), although the heart may still be beating for a certain time. During live donor transplantation, it must be noted that only the organs capable of regenerating (bone marrow, liver, skin), or a paired organ (kidneys) needs to be chosen for transplantation. Although an organ transplantation procedure is undertaken to save a human life, protecting the rights of the donors assumes increased significance. The donor's life should not be placed at risk due to organ donation. Therefore, transplantations should only be attempted after carefully considering the potential benefits against the foreseeable risks both to the donors and the recipients and the donor's health must be given high priority.

Voluntary informed consent of the donor must be obtained after informing in detail about the potential risks to him/her after the transplantation. Since getting/finding a voluntary donor is very difficult and the transplantation is a costly affair, scientists may be forced to create/clone human beings, which is against the ethical principles laid down by the international regulatory bodies. Recently, increased awareness has spread among the literate people regarding the importance of organ donation after death. There are now special drives for encouraging people to donate their organs after death, and such a will can be communicated to family members or the hospitals as a "living will" (consent to donate their organs after death while still alive with a witness of two or more people/family members).

Such transplantation procedures are undertaken solely for saving the lives of people and should never be

associated with any financial benefits. Cases of embryonic stem cell transplantations from the aborted fetus, dead fetus, and neonates are all governed by the local and international ethics (IEC) guidelines and the regulatory bodies like the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT), and the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). Rather than research, transplantation is a surgical procedure, which is undertaken to protect the life of a human being. It involves the grafting of a human organ from a donor. Such a process is very critical both in terms of medical and ethical reasons. Transplantations can be of various types like live donor transplantation (related/unrelated), cadaveric transplantation (organ transplantation from a dead person), fetal organ transplantation (embryonic stem cells), neural transplantations, bone marrow transplants, xeno-transplantation (animal tissue/organs) [11]. The informed consent in such procedures may be influenced by the financial benefits. Besides, during cadaveric transplants, the person's consent is not available. Defining death, especially the term 'brain dead' is not completely understood in society and could be misused [11].

Because of a big gap between the demand and supply of organs for transplantation, there is an increased significance of the ethical concerns related to organ transplantation procedures. The major ethical issues concerning transplantations stem from the description of death (brain dead), informed consent of a live donor, financial obligations related to the transplantation procedures, ethical concerns of donor registries, the international organ trade, issues with the allocation of the organs, and waitlist [12].

7. Ethical Considerations for Assisted Reproductive Technologies

There are several concerns related to the legitimacy of the children born through assisted reproductive technology (ART). The process of the in-vitro fertilization technology (IVF), the surrogate motherhood, and the procedures for the preservation, utilization, and disposal of unused embryos is very critical. During the process of ART, the sperm or the ovum is acquired from the sperm/ovum banks. The child born in such a way legally belongs to the parents and in no way will be related to the sperm/ovum donors. Also, it is the laboratory's responsibility to make sure that confidentiality is maintained. If sperm and the ovum are collected from the parents (married couple) themselves, there will be no need for medico-legal considerations. When the IVF is combined with the embryo transfer (IVF-ET), and in cases where the sperm/ovum is donated, and the embryo is implanted in a different womb (surrogate), there will be different parental origins, which in turn increases the ethical, and medico-legal concerns. The IVF, ART, and surrogacy pose increased ethical concerns. Surrogacy may be wrongly utilized by the financially sound parties by influencing the surrogate mother using financial inducements. In surrogacy, the women, her husband need to give their consent to carry the embryo until the child's delivery and would hand over the child to the genetic parents.

If a problem arises about the child's future, DNA fingerprinting technology may be used to confirm the parenthood, where surrogate mother/parents don't match with the child's genetic make-up. All the records containing the complete details of the source of the sperm/ovum, the parents who agreed for surrogacy must be maintained, which would form the documents for verification in the future. The IVF and the ART may be performed and monitored by qualified personnel and a decision of surrogacy must be taken only after thorough genetic counseling, screening, and medical reasons justifying the inability to carry the embryo. Surrogacy is a complete legal contract, where the mother is appropriately compensated both during the pregnancy and the delivery. The preservation periods of the embryos are specified both locally (Indian council for medical research (ICMR) and internationally (WHO). In the United Kingdom, the embryos may be stored in a frozen state for 10 years and the semen may be frozen for five years. In general terms, it is not approved to use an embryo after 14 days of formation.

Although assisted reproductive technology (ART) is instrumental in solving fertility issues, it had thrown several challenges in terms of ethical, legal, and social concerns. The most significant factor is the issue of financial implications, where the ART may be more accessible to people with increased financial strengths. Ethical concerns are also expected concerning the embryonic genetic screening and diagnosis, donor gametes (sperms, oocytes), embryo donation, surrogacy, and gestational carriers, and most significantly, the potential harm that the ART itself may pose to the individuals [13]. The Indian scenario is quite intriguing, where on one side, there is an increase in the ART capabilities, and on the other side, there is a lack of standardization of the procedures. Furthermore, in India, the reporting mechanism regarding the conduction of ART is not adequate. It was recommended that there should be an ART registry in place for guidance on the standardization of the protocols and to improve [14].

8. Ethical Considerations and Guidelines for Clinical Research among Geriatric Population

Because clinical research is critical for the advancement of medicine and improvement of public health, and it involves human participants, many ethical issues may be associated with such type of research. The ICH prescribes harmonized tripartite guidelines for the conduction of clinical research among various groups/types of populations. In this concept, we understand the ICH harmonized tripartite guidelines concerning geriatric people (age greater than 65 years). Geriatric age group people are sensitive to medical interventions due to extreme age, co-morbid conditions, and drug interactions. Age-related diseases like Alzheimer's and heart diseases are common among the geriatric group and clinical research in this area benefits such people. Since old age may compromise the functions of the organs like the liver, kidneys, the clinical research trials involving newer

drugs/new combinations of the older approved drugs/formulations may pose potential risks to the participant's health. While initiating clinical research among the geriatric population, it is important to recruit subjects with ages greater than 75 years, and those who have co-morbidities. Also, it is important to include younger age group subjects and compare the activities of the newer drug among the geriatric population.

It is recommended that the geriatric age subjects must be included in phase II and phase III stages of clinical research. Also, a productive result/meaningful comparison is expected when more than or at least 100 geriatric age participants are recruited. The basic knowledge that a researcher acquires by including both the older and younger age groups is that it facilitates the understanding of the role of the proper functioning of organs like the liver and the kidneys, which are required for drug metabolism, absorption, and excretion (pharmacokinetics). It is recommended that the pharmacokinetic studies are preferably performed in the healthy geriatric population or diseased people. To improve the knowledge of the pharmacokinetics of the drugs, the researchers must include both the young and the geriatric population with hepatic and renal diseases. To study the pharmacodynamics (therapeutic response to different doses of drugs, side effects at varied drug concentrations), the geriatric age people are recruited except in cases while testing sedative, hypnotic, and anti-psychotic/psychoactive drug candidates. People with an age of more than 65 years may be categorized as the geriatric age group. This age group is considered the fast-growing age group around the world. The geriatric age group forms a significant portion of the patients who present to the hospital for healthcare needs. Most clinical trials fail to recruit people in the geriatric age group, although this age group forms a significant chunk among the people who consume medications for various causes that may include cardiovascular diseases, arthritis, Parkinson's disease, Alzheimer's disease, and cancer.

The developed nations and the regulatory authorities in such countries have already initiated mechanisms to include the geriatric age group in the clinical trials unless there is a valid reason to exclude them. The scenario is not very good in developing nations including India, where the CDSCO is yet to liberalize the age limit that is in place for various drug-related clinical research trials [15]. It was in 2010, that the ICH E7 Guideline, which deals with the clinical research concerning the geriatric age group was revised. This revision had relevant information that considers the rapidly growing geriatric age group population. Regulatory recommendations from the ICH formulated the guideline and recommend the inclusion of geriatric age people in various clinical research trials [16].

9. Ethical Considerations and Guidelines among Pediatric Population

The clinical research trials are critical among various age groups, and the pediatric age is among the most sensitive. Because of the sensitivities associated with the clinical research in the pediatric age group, there are only fewer drugs approved for pediatric use. Therefore, there is

an increased necessity for the development of pediatric medical products throughout the world. The ICH guidelines for clinical research in the pediatric age group facilitate the safe, efficient, and ethical study of medicinal products. The ICH guidelines concerning various clinical research concerns in the pediatric population are presented in [Table 6](#).

Table 6. List of ICH documents with relevant information impacting on pediatric studies

S.No	ICH code	Governing Topic
1	E2	Clinical safety data management
2	E3	Structure and Content of Clinical study Reports
3	E4	Dose-Response Information to Support Drug Registration
4	E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
5	E6	Good Clinical Practice: Consolidated Guideline
6	E8	General Considerations for Clinical Trials
7	E9	Statistical principles of clinical trials
8	E10	Choice of Control Groups in Clinical Trials
9	M3	Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
10	Q1	Stability testing
11	Q2	Validation of analytical procedures
12	Q3	Impurity testing

Among the general principles recommended by the ICH concerning the pediatric population, “the medicines prescribed for pediatric use must be appropriately evaluated before use” appears to be the most significant. It is recommended that in any clinical research trial, a pediatric group should be included which is important to obtain the knowledge of the effects of drugs and may facilitate the use of a drug in such populations in the future. The clinical research on the pediatric population must be done responsibly, and according to the local and international guidelines. The companies, regulatory authorities, health professionals, and society should take responsibility for clinical research in the pediatric population.

Clinical research for the drug development process in the pediatric population should consider the nature/seriousness of the clinical condition to be treated, its prevalence, effectiveness, and adverse effects of the currently available drugs for the same condition, development of pediatric-specific endpoints, and the pediatric age range to be included for testing. Another important consideration while conducting clinical research trial includes the development of pediatric formulations which provides dose accuracy and increase drug compliance. Different types of drug formulations are developed for pediatric use that includes liquids, suspensions, chewable tablets, injectable formulations. The oral formulations must be developed in flavors and colors, which may be more acceptable for pediatric use.

Clinical research involving the pediatric population poses a unique scenario that is encountered with the adult population. Research including the children pose issues with informed consent and is considered very crucial. Due to this factor, several clinical research studies fail to

adequately represent the age group and therefore, the safety, efficacy of drugs that are used are not completely clear. The Standards for Research (StaR) in Child Health, promulgated by the USA and the European Union in the year 2009, had proposed aims to improve the design, conduct, and reporting of clinical research trials in the pediatric age population [17]. A recent report had observed that one out of five clinical research trials among the pediatric population fails because of the faulty study design, lack of experiment planning, and inadequate participant enrolment. This study had highlighted the significance of planning clinical research concerning the modes of administration of the drugs, dosage studies, monitoring, and safety studies, apart from the ethics of recruitment and informed consent [18].

10. Ethical Considerations and Guidelines for Vaccines and Diagnostic Devices

There are various phases of clinical trials that include the phases of the vaccine trial, clinical trials involving the surgical procedure, and diagnostic methods, and the clinical trials involving the herbal source medical products. The clinical research with regards to the vaccine trials is like the clinical research drug trials with some mild differences. During phase I of a drug trial, the IND is given to healthy people (30) for understanding its tolerability and safety. Similarly, in a vaccine trial, the vaccine is given to low-risk people to study the immunogenicity, safety, and other biological consequences/effects. The study also examines the safety and effectiveness of the routes of administration of the vaccine. In phase II trial of a drug trial around 100 healthy subjects are recruited, whereas, in a vaccine trial, one can choose to include healthy/low-risk people to administer the vaccine (prophylactic) or choose high-risk/diseased people for vaccine administration (therapeutic). This phase majorly examines the effectiveness of the vaccine in a trial. Under phase III of a vaccine trial, the vaccine is administered to thousands of people, usually, high-risk groups, and examine its efficacy in terms of immunogenicity and its ability to prevent disease transmission.

Although a vaccine trial is very important from the public health perspective, the sponsor and the investigators of the study must ensure that the clinical research is carried out following the principles, and guidelines laid down by the Drug Controller General of India (DCGI), Department of Biotechnology (DBT) and the Ministry of Environment and Genetic Engineering Approval Committee (GEAC). The sponsor and the investigators must be cautious during the vaccine trial involving a live/live attenuated vaccine. Because such vaccines may pose potential risks of infections to the volunteers/participants/study subjects, they should be adequately informed about the consequences, and informed consent is duly obtained from all the participants. Concerning the clinical research involving surgical procedures/devices, diagnostic devices/bio-equipment, which is an emerging field of research in India, the

policies on regulation of such research are still a novice. Only the needle and syringe manufacture has been till now governed by the DCA, 1940 act. The medical devices include both the critical (catheters, implants like the pacemakers, stents, etc.) and non-critical (thermometer, blood pressure apparatus, etc.) devices, and all these are considered inert and are not considered therapeutic. Only recently the Indian Medical Devices Regulatory Authority (IMDRA) has been constituted as a regulatory authority with regards to the manufacture of medical/surgical devices. The IMRDA regulations are constituted by the Society of Biomedical Technology (SBMT) under the Defence Research Development Organization (DRDO).

Stringent ethics consideration must be given regarding the exposure of the study participants to radio-active chemicals, X-rays, and other herbal medicinal products. The radiation exposures must be performed following the regulatory authority (like the Bhabha Atomic Research Centre, Mumbai (BARC)). The regulatory requirements for the conduction of clinical research in the development of vaccines, and diagnostic devices, as recommended by the WHO include Good Manufacturing Practice (GMP) for drugs/medical products, biologicals, regulation, and licensing of biological products in countries with newly developing regulatory authorities, and guidelines for national authorities on quality assurance for biological products [20]. Violation of human rights concerning the informed consent and the conduction of clinical trial in human papillomavirus (HPV) vaccine trial which included 24,000 schoolgirls surfaced in India in 2009. This case highlights the lack of human rights protection of the study participants [21].

The international covenant on economic, social, and cultural rights (ICESCR) defines that the right to health includes the right to control their health, the right to be free from interference, torture, and irresponsible medical treatment/experimentation. It also stresses the need for considering the benefits to risks before initiation of a trial and ensuring regular participant health monitoring both during and after the clinical research trial.

11. Current Perspectives

Because the research involving the human subjects was being carried out for several decades, and that the responsibility of the safety and well-being of the participating patient was completely in the hands of the physician/clinician (taking the Hippocratic oath) treating the patient, not much was looked into the ethical considerations beyond this aspect (medical ethics). But, as time passed by, and after considering the incidents like the Nazi's mishandling the soldiers at the Nuremberg during the second world war, the need for separate ethics, research ethics, and the relevant guidelines have emerged [22]. Since the clinical research with randomize-controlled trial (RCT) experimentation results in improved results, and data accuracy, such type of clinical research is regarded as the best. There are several types of randomization techniques like the simple randomization, block randomization (creating blocks of the participants and randomizing each block to improve the study balance and results), restricted randomization (unbalanced

randomization, where the patients are recruited only after considering their interest in the study and rule out dropouts), stratified (to minimize the imbalances concerning the prognostic factors, that may include the sex, site of the study, etc. and thus minimize the imbalances), and adaptive randomization (consider a change in the allocation of the drug after having known its therapeutic effects and minimize the imbalance) [23]. The medical graduates, during their dissertation study, take up the projects that involve human participants. Therefore, they need to understand the significance of the principles of clinical research involving human subjects and the value of a well-designed informed consent, and the in-depth process of obtaining it from all the study participants. A recent study had noted that although the medical post-graduates have enough knowledge on the aspects of informed consent, there is a need for regular continuing medical education (CME) programs, and workshops to update them [24]. The CDSCO of India launched the materiovigilance program (MvPI) at the Indian Pharmacopeia Commission (IPC), Ghaziabad in the year 2015 with the principal aims to oversee the medical device-associated adverse events (MDAE), sensitize the healthcare workers regarding the adverse event reporting, generate reliable safety, efficacy, and performance data, and report the information to the regulatory authorities which take the decisions on the approval and marketing of the products [25].

A new strategy to improve the social value of global health research, where research is conducted in multicentre at different countries was proposed in low-income countries. This promulgates benefit-sharing as a key strategy to address the moral issues relevant to the individuals, the communities, and the respective countries [26].

In the epidemiological research concerning the surveillance of infectious diseases like the Influenza virus, it is important to address the relevant ethical concerns. Epidemiological research studies the distribution and determinants of the diseases. Epidemiological studies are also undertaken to understand the disease mechanisms, diagnosis and prognostic efficacy, efficacy of new therapeutic interventions, and most significantly, to understand the association between the exposures and outcome [27]. The concept of clinical research was previously confined predominantly to the developed countries, majorly because of financial constraints. But, in recent times, the developing nations have been actively involved in clinical research owing to the advantages to the availability of the varied population, and the health benefits to the people and the community as a whole [28]. The ethical considerations become even more significant during the research on psychiatric patients. Informed consent in such type of research becomes critical and should be carefully obtained from the participating patients after evaluating the clinical, ethical, and legal aspects. As per the Mental Healthcare Act (MHCA) 2017, and the ICMR's the National Ethical Guidelines for Biomedical and Health Research involving Human Participant for research protocols, and informed consent indicating the patients/participants autonomy to participate in the study that includes admission, treatment, planning, and research interventions, and other procedures are essential [29].

Apart from the regular clinical research, there may be occasions where an unapproved drug (safety and efficacy are not known) needs to be administered to the study participants (compassionate use). The compassionate use of the drugs (after phase III clinical trials) is a situation that arises when the patients are suffering from potentially life-threatening diseases, and the regular therapeutic options are not effective enough to treat. It has been noted that in any such situations the approval of the ethics committee remains the mainstay before the study is initiated. A well-designed informed consent delineating the necessary information about the compassionate drug, its potential foreseeable and un-foreseeable adverse effects, and other information concerning the modes of administration, compensation terms, and benefits may be instrumental in safeguarding the patients' rights and protect him/her from abuse [30]. The informed consent may be waived off under some special circumstances, and it may be difficult/tricky to obtain informed consent from the vulnerable population like the pregnant women, the fetuses, children, orphans, employees, army personnel/soldiers, psychologically imbalanced and terminally ill people [31]. During the ART therapeutics, it has been noted that there is a chance for the excess embryos which were collected from one donor to be wrongly utilized. Such supernumerary embryos are either cryopreserved or utilized to treat a different couple for infertility. In the Indian couples, it was observed that they preferred to donate the excess embryos rather than their disposition [32]. A recent research report had evaluated the documents related to the pharmacokinetics, safety, and efficacy of the drugs regarding the geriatric population when a drug is under evaluation for approval at the Food and Drug Administration (FDA). This study has noted that the data relevant to the use of drugs in the geriatric age group was insufficient and needs improvement [33].

12. Conclusion

The involvement of human participants in the clinical research is associated with increased risk and health implications among study participants. Therefore, clinical studies are screened and thoroughly monitored by the local, national, and international regulatory agencies. The institutional ethics committees ensure that the studies are appropriately designed, and participants are recruited voluntarily and after informed consent. The pediatric population, and the geriatric age group, along with other vulnerable groups like the pregnant women, and their representation in clinical trials is not adequately addressed over a period. With the availability of increased scientific technologies, and improved infrastructure, vaccine, and device development clinical studies have become feasible. However, such clinical trials should be cautiously undertaken after carefully evaluating the ethical considerations as discussed comprehensively in this article.

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