Regulatory Prospective of Clinical trial

Clinical trials are a fundamental part of clinical research that support the development of new medicines or uses of existing medicines. Well designed and conducted clinical trials help answer key questions in health care and drug development. Their results are essential for evidence-based healthcare decisions.

New drug development can improve quality and lifespan of patient. As clinical trial play's important role in development of new drug, government is trying to safeguard that the safety as well as rights of the human subjects are secure, and the quality of the trials completed in India expand to international standards. Indian regulation has set guidelines for informed consent, compensation in case of injury or death and serious adverse events (SAEs) reporting. The clinical trials which are performed in India should comply with schedule Y of Drugs and Cosmetics Act and International Committee of Harmonization-Good Clinical Practices (ICH-GCP) Guidelines for clinical trials.

INTRODUCTION

ICH denotes for "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human consumption".
symbolizing the letters "I", "C", "H" in a manner which embodies the letters in an outline human form. The main colour of the logo is blue, a colour often used for healthcare.

ICH mission:

ICH's mission is to make suggestions towards accomplishing greater harmonization in the interpretation and application of technical Guidelines and requirements for medicinal product registration.

Purpose of ICH

Promotion of public health through international harmonization that contributes to:

- Prevention of unnecessary duplication of clinical trials and post market clinical evaluations.
- Development and manufacturing of new medicines
- Registration and supervision of new medicines
- Reduction of unnecessary animal testing without compromising safety and effectiveness Accomplished through Technical Guidelines that are implemented by the regulatory authorities.

History of ICH:

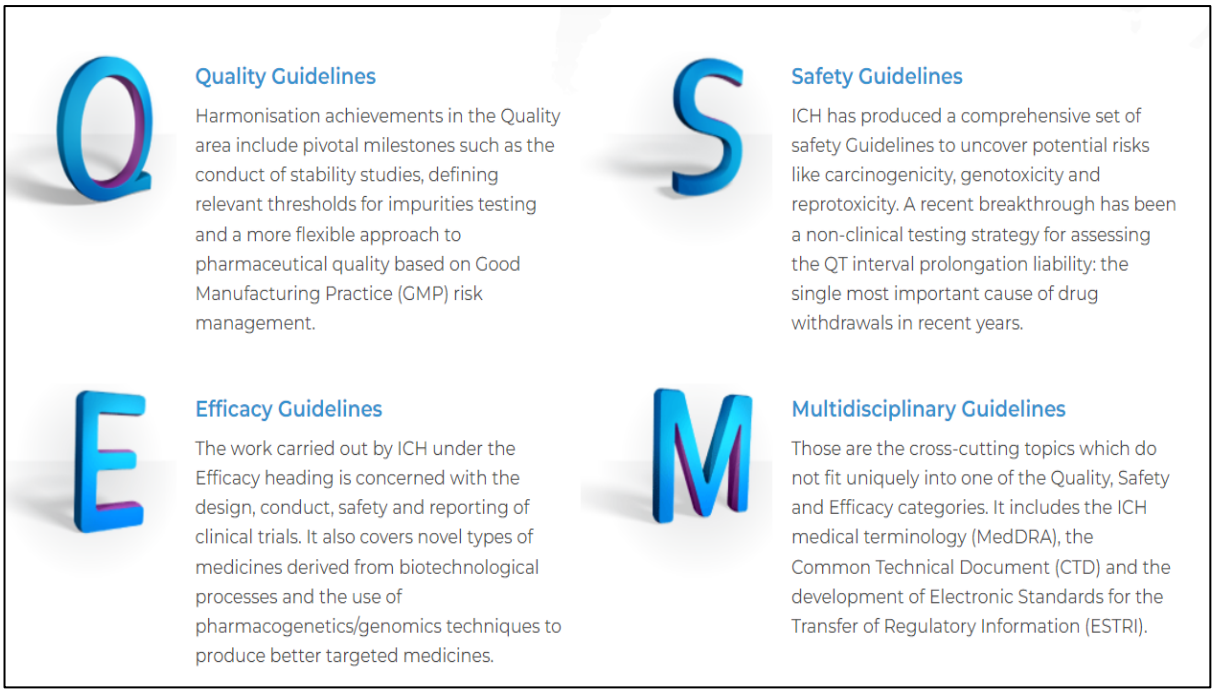
Since ICH's origin in 1990, the ICH process has step by step evolved. ICH's first 10 years saw substantial progress in the growth of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics (QSEM). Work was also undertaken on several important multidisciplinary subjects, which admitted MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).

As the second tenner the exploitation of ICH Guidelines continued, but with more care given to the following need to:

- Maintain already present Guidelines as science and technology continued to develop.
- Expand communication and spreading of information on ICH Guidelines with non-ICH regions became a key focus.
- Provide the implementation of ICH Guidelines in ICH's own regions.

Entering its third tenner of activity, ICH's attention is directed towards continuing the benefits of harmonization outside the ICH regions. Training, active participation of non-ICH regions in Guideline exploitation is seen as key in this effort.

Overview of ICH Guidelines:



INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

It was finalized in 1996 and became effective in 1997 but was not enforced by law at that time. The Medicines for Human Use (Clinical Trials) Regulations 2004 and the European Union (EU) Directive on Good Clinical Practice changed the world perspective, and compliance with GCP is now a legal obligation in the UK/Europe for all trials involving the investigation of medicinal products.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

THE PRINCIPLES OF ICH GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.
3. Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants are well-informed.
4. Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).
5. Clinical trials should be scientifically sound for their intended purpose, and based on robust and current scientific knowledge and approaches.
6. Clinical trials should be designed and conducted by qualified individuals.
7. Quality should be built into the scientific and operational design and conduct of clinical trials..
8. Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.
9. Clinical trials should be described in a clear, concise, and operationally feasible protocol.
10. Clinical trials should generate reliable results.
11. Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately.

12. Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

These principles are self-explanatory and, when summarized, simply mean:

All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risks. The rights, safety and well-being of trial participants are of paramount importance, and these should be preserved by obtaining informed consent and maintaining confidentiality. The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification, and interpretation. Investigational products should be manufactured according to Good Manufacturing Practice.

Organization

ICH Steering Committee and its subgroups The ICH Steering Committee and its sub-groups are constituted of representatives from 6 parties that represent the regulatory bodies and research-based industry in the USA, Japan, and the European Union.

Ethical Committee: Institutional Review Board, Ethical Guidelines for

Region	Regulatory Body	Research Based Industry
Japan	**MHLW** - Ministry of Health, Labour and Welfare	**JPMA** - Japan Pharmaceutical Manufacturers Association
Europe	**EU** - European Union	**EFPIA** - European Federation of Pharmaceutical Industries and Associations
USA	**FDA** - Food and Drug Administration	**PhRMA** - Pharmaceutical Research and Manufacturers of America

Biomedical research and Human participants.

Amendments to Drugs and Cosmetics Rules were published vide G.S.R.72 (E) dated 08.02.2013 specifying the requirements and guidelines for registration of Ethics Committee and re-registration under Rule 122DD to the Drugs and Cosmetics Rules 1945.

For the purpose of the Rule 122DD, an Ethics Committee is a committee comprising of medical, scientific, non-medical and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and it shall be responsible for

reviewing and approving the protocol, the suitability of the investigators, facilities, methods and adequacy of information to be used for obtaining and documenting informed consent of the study subjects and adequacy of confidentiality safeguards. In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyze and forward its opinion as per procedure specified under APPENDIX XII of Schedule Y.

The Ethics Committee shall allow inspectors or officials authorized by the Central Drugs Standard Control Organization to enter its premises to inspect any record, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be in relation to the conduct of clinical trial.

If the Ethics Committee fails to comply with any of the conditions of registration, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefor, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.

Institutional Review Board

Institutional Review Board (IRB) An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects

The IRB/IEC should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities. The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following: - approval/favorable opinion; - modifications required prior to its approval/favorable opinion; - disapproval / negative opinion; and - termination/suspension of any prior approval/favorable opinion.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

The first International Code of Ethics for Research involving human subjects 'The Nuremberg Code' was a response to the cruelties committed by Nazi Research Physicians revealed at the Nuremberg war crimes trials. Thus, it was to prevent any repetitions by physician of such attacks on the rights and welfare of human

beings that human research ethics came into being. The Nuremberg (1947) laid down standards for carrying out human experimentations, emphasizing the subject's voluntary consent. World Medical Association (1964) took a step further to reassure society by adopting the 'Declaration of Helsinki', which laid down the ethical guidelines for research involving human subjects.

Ethical Guidelines for Biomedical research and Human participants.

In October 2017, the Indian Council of Medical Research issued the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. The purpose of these guidelines is to safeguard the dignity, rights, safety and well-being of the human participants involved in biomedical and health research. These guidelines must be followed by all stakeholders including institutions, ethics committees (ECs), researchers and sponsors/ funding agencies.

Every research has some inherent probabilities of harm or risk and thus, protection of research participants and/or communities should be built into the design of the study.

While conducting biomedical and health research, the four basic principles namely; respect for persons (autonomy), beneficence, non-maleficence and justice must guide research in order to protect the dignity, rights, safety and well-being of research participants.

ECs must ensure that the research is conducted in accordance with the basic principles.

1. All biomedical researches on human subjects should be absolutely essential after a due consideration of all alternatives for the advancement of knowledge and human beings (Principle of Essentiality).
2. The concept of voluntariness and informed consent shall apply to the community as a whole and to each individual member who is subject of research (Principle of voluntariness and Informed Consent).
3. Irrespective of the socio-economic status and educational levels, research subject should be fully appraised of all risks arising as a result of research (Principle of Non-exploitation).
4. The identity of records of human subjects of research should be kept confidential and should not be disclosed without valid scientific and legal reasons (Principle of Privacy and Confidentiality).
5. Due care and caution is taken to ensure that research subjects are put to minimum risks no irreversible risks (Principle of Precautions and Risks Minimization).
6. The Research is conducted at all times by the competent and qualified persons (Principle of Professional Competence).

7. The research is committed in a fair, honest, impartial and transparent manner and records and data are maintained for a reasonable period (Principle of Accountability and Transparency).
8. The research is conducted to benefit all human kind and not just socially better off. (Principal maximization of Public Interest and of Distributive Justice).
9. All institutional arrangements required to be made in respect of research are made in a bonafide and transparent manner and records are properly maintained and preserved. (Principle of Institutional Arrangements).
10. After due experimentation and due evaluation, results are brought into public domain through scientific and other publications under the law in force at that time (Principle of Public Domain).
11. It is the responsibility of all directly and indirectly involved with the research to monitor, review constantly and take remedial action at all stages of research (Principle of Totality and Responsibility).
12. All persons concerned directly and indirectly should scrupulously observe the laid down rules, guidelines, norms, directions (Principle of Compliance).

There are some general issues that must be kept in focus during the conduct of biomedical and health research involving human participants

Researchers must protect the dignity, rights, safety and well-being of research participants. They should have appropriate qualifications, competence in research methodology and be compliant towards the scientific, medical, ethical, legal and social requirements of research. The researcher, sponsor and EC must conduct a benefit–risk assessment and actively attempt to maximize benefits and minimize risks to participants. Benefits to the individual, community or society refer to any sort of

Benefit–risk assessment	Informed consent process	Privacy and confidentiality
Distributive justice	Payment for participation	Compensation for research related harm
Ancillary care	Conflict of interest	Selection of vulnerable and special groups as research participants
Community engagement	Post-research access and benefit sharing	

Table:

favorable outcome of the research, whether direct or indirect. The social and scientific value of research should justify the risk, which is the probability of

causing discomfort or harm anticipated as physical, psychological, social, economic or legal.

Risk can be categorized as less than minimal risk, minimal risk, minor increase over minimal or low risk and more than minimal or high risk. The EC must decide about the type of review required (exempted, expedited, full committee) based on the type of risk involved.

The researcher must obtain informed consent from the participant/legally acceptable/ authorized representative (LAR) in writing.

Informed consent documents (participant information sheet and informed consent form) should carry the specified elements in simple, layman's language. These documents should be approved by the EC.

Oral consent/waiver of consent/re-consent may be obtained under certain conditions, after due approval by the EC. Researcher(s) should safeguard the privacy and confidentiality of participants and research-related data from unauthorized access. Benefits and burdens of research should be equitably distributed among the participating individuals or communities.

Participants should not be made to pay for research-related expenses incurred beyond routine clinical care. Reimbursement for expenses incurred can be made in cash or kind or both. The researcher must report all serious adverse events (SAEs) to the EC within 24 hours of knowledge and submit a report on SAE relatedness to research within 14 days.

Research participants who suffer direct physical, psychological, social, legal or economic harm are entitled to financial compensation or other forms of assistance. It is the responsibility of the sponsor (whether a pharmaceutical company, government or non-governmental organization (NGO), national or international/bilateral/multilateral donor agency/institution) to include insurance coverage or provision for possible compensation for research related injury or harm within the budget.

In investigator initiated/student research, the investigator/institution where the research is conducted becomes the sponsor and must provide compensation for research-related injury through insurance, corpus funds or grants. Free medical care may be offered as ancillary care for non-research-related conditions or incidental findings if it does not amount to undue inducement as determined by EC.

Policies for declaration and management of financial or non-financial (personal, academic or political) conflict of interest for researchers, EC, institution and sponsor must be implemented by research institutes. The selection of vulnerable and special groups needs careful consideration, with provisions for additional safeguards and close monitoring.

Engaging with the community from the beginning of research till after its completion helps to improve design and conduct of research and ensures greater

responsiveness to health needs. However, every individual participant's consent is essential. Post-research access and benefit-sharing may be done with individuals, communities and populations, wherever applicable after completion of study.

Overview of ICMR

The Indian Council of Medical Research (ICMR), New Delhi, the apex body in India for the formulation, coordination and promotion of biomedical research, is one of the oldest medical research bodies in the world (more than hundred years in the service of bio-medical research). As early as in 1911, the Government of India set up the Indian Research Fund Association (IRFA) with the specific objective of sponsoring and coordinating medical research in the country. After independence, several important changes were made in the organization and the activities of the IRFA. It was re-designated in 1949 as the Indian Council of Medical Research (ICMR) with considerably expanded scope of functions. The ICMR is funded by the Department of Health Research (DHR), Ministry of Health & Family Welfare, Government of India. It promotes research in all areas of medical and related science with an aim of improving the health and quality of life of the Indian public. The Council has broadened its activities from a pure biomedical research organization to one that also undertakes health systems research. It's mandate covers the entire spectrum of research from biological to social, laboratory to field, and from idea to use. The Council commits itself to take its research agenda forward, and strives to get research results translated into efficient disease control and prevention strategies.

The Council's research priorities coincide with the national health priorities such as control and management of communicable diseases, fertility control, maternal and child health, control of nutritional disorders, developing alternative strategies for health care delivery, containment within safety limits of environmental and occupational health problems, research on major noncommunicable diseases like cancer, cardiovascular diseases, blindness, diabetes and other metabolic and hematological disorders, mental health research and drug research (including traditional remedies). All these efforts are undertaken with a view to reduce the total burden of disease and to promote health and well-being of the population. In the context of the changing public health scene, the balancing of research efforts between different competing fields, especially when resources are severely limited, is a typical problem encountered in the management of medical research, particularly in developing countries. Infectious diseases and excessive population growth have continued to constitute the major priorities to be addressed in medical research throughout the past several decades. In addition to tackling these issues, in recent years, research has been intensified progressively on emerging health problems such as cardiovascular diseases, metabolic disorders (including diabetes mellitus), mental health problems, neurological disorders, blindness, liver diseases, hearing impairment, cancer, drug abuse, accidents, disabilities etc. Research on traditional medicine/herbal remedies was revived with a disease-oriented approach. Attempts have been made to strengthen and streamline medical informatics and communication to meet the growing demands

and needs of the biomedical community. The Council is alert to new diseases and new dimensions of existing diseases, as exemplified by the rapid organization of a network of Surveillance Centers for AIDS in different states of India in 1986. The Governing Council of ICMR is presided over by the Union Minister for Health & Family Welfare, GoI. It is assisted in scientific and technical matters by a Scientific Advisory Board comprising of eminent experts in different biomedical disciplines. The Board, in its turn, is assisted by a series of Scientific Advisory Groups, Scientific Advisory Committees, Expert Groups, Task Forces and Steering Committees etc. which evaluate and monitor different research activities of the Council.

The ICMR promotes biomedical research in the country through intramural as well as extramural research.

1. Intramural research is carried out currently through the Council's 32 Research Institutes/ Centres/Units. These include: a) 21 mission-oriented national institutes located in different parts of India that address the research on specific areas such as tuberculosis, leprosy, cholera and diarrhoeal diseases, viral diseases including AIDS, malaria, kala-azar, vector control, nutrition, reproduction, immunohaematology, oncology, medical statistics, etc; b) 6 Regional Medical Research Centres that address regional health problems, and also aim to strengthen or generate research capabilities in different geographic areas of the country; and c) 5 Units/Centres dealing with food & drug toxicology, viral diseases, handling microorganisms of highly infectious nature, prenatal diagnosis for neonatal retardation etc and supply of various animal models and feeds for experimental purposes.

2. Over the decades, the base of extramural research and also its strategies have been expanded by the Council. Extramural research is promoted by ICMR through: a) Setting up of centers for Advanced Research in different research areas around existing expertise and infrastructure in selected departments of Medical Colleges, Universities and other non-ICMR Research Institutes. b) Task force studies which emphasize a time-bound, goal-oriented approach with clearly defined targets, specific time frames, tbl-standardized and uniform methodologies, and often a multi-centric structure. c) Open-ended research on the basis of applications for grants-in-aid received from scientists in non-ICMR Research Institutes, Medical colleges, Universities etc. located in different parts of the country.

3. In addition to research activities, the ICMR encourages human resource development in biomedical research through: a) Research Fellowships b) Short-Term Visiting Fellowships c) Short-Term Research Studentships d) Various Training Programmes and Workshops conducted by ICMR Institutes and Headquarters Indian Council of Medical Research 5 Overview of ICMR 4. For retired medica

4. For retired medical scientists and teachers, the Council offers the position of Emeritus Scientist to enable them to continue or take up research on specific

biomedical topics. The Council also awards prizes to Indian scientists, in recognition of significant contributions to biomedical research. At present, the Council offers 38 awards, of which 11 are meant exclusively for young scientists (below 40 years).

Informed Consent Processes

Voluntary written informed consent should be obtained in an informed consent document (ICD) from each participant to protect each individual's freedom of choice. Informed consent is a continuous process involving three main components:

• Providing relevant information to potential participants

• Ensuring competence and comprehension of the information and

Elements of an ICD	Additional elements (optional)
1. Statement mentioning that it is research	1. Alternative procedures or treatment
2. Purpose and methods	2. Insurance coverage
3. Duration, frequency, methods	3. Possible stigmatizing condition
4. Benefits to participant, community or others	4. Biological material and data, including:
5. Foreseeable risks, discomfort or inconvenience	i) Current and future uses
6. Confidentiality of records	ii) Period of storage and secondary use
7. Payment/reimbursement for participation	iii) Sharing of data and biological materials
8. Treatment and/or compensation for injury	iv) Right to prevent use of biological sample
9. Freedom to participate/withdraw	v) Provisions to safeguard confidentiality
10. Identity of research team and contact persons	vi) Post-research plan/benefit sharing
	vii) Publication plan/photographs/pedigrees

• Voluntariness of participation

Table: Characteristics of an ICD

Researchers should only use the EC approved version of the consent form and its translation in local languages. Informed consent should be voluntary and be signed by the participant after receiving information, understanding it and discussing with family/friends (if required).

Verbal/oral consent/waiver of consent/reconsent may be obtained only after approval by the EC. Table 6 gives conditions for granting waiver of consent. Appropriate ICD should be prepared for differently abled participants. In case of research involving children, in addition to parental consent, verbal (7-12 years) or simplified written (>12 – 18 years) assent should also be taken from the participant.

The LAR's consent is required in case a participant is incompetent (medically or legally). Electronic/online consent may be obtained for research involving sensitive topics while safeguarding information and data and also if required for regulatory clinical trials. Individual consent is important and required, even if the community gives permission for participation in a research study.

In studies using deception a true informed consent may lead to modification and may defeat the purpose of research. Such research should be carefully reviewed by the EC before implementation. In such instances, an attempt should be made to debrief the participants/communities after completion of the research.

Table: Conditions for granting waiver of consent

The EC may grant consent waiver in the following situations:
• research cannot practically be carried out without the waiver and the waiver is scientifically justified;
• retrospective studies, where the participants are de-identified or cannot be contacted;
• research on anonymized biological samples/data;
• certain types of public health studies/surveillance programmes/programme evaluation studies;
• research on data available in the public domain; or
• research during humanitarian emergencies and disasters, when the participant may not be in a position to give consent. Attempt should be made to obtain the participant's consent at the earliest.

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