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CLINICAL RESEARCH AND GOOD CLINICAL PRACTICES - A REVIEW

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ABSTRACT

Overview to Clinical Research involving human subjects can be described as either observational or experimental. And Explanation to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Enlisted all Guidelines to Good Clinical Practices, Quality, Safety, Efficacy, Multidisciplinary Guidelines. Important principles to conduct a Clinical Trial.

Key words: Clinical Research, ICH, Clinical Trial.

INTRODUCTION

Overview to Clinical Research

- Clinical research, research involving human subjects, can be described as either observational or experimental. The findings of all clinical research can be threatened by issues of bias and confounding. Biases are systematic errors in how study subjects are selected or measured, which result in false inferences.
- Confounding is a distortion in findings that is attributable to mixing variable effects. Uncontrolled observation research is generally more prone to bias and confounding than experimental research.
- Observational research includes designs such as the cohort study, case-control study, and cross-sectional study, while experimental research typically involves a randomized controlled trial (RCT).
- The cohort study, which includes the RCT, defines subject allocation on the basis of exposure interest (e.g., drug, disease-management program) and follows the patients to assess the outcomes.
- The case-control study uses the primary outcome of interest (e.g., adverse event) to define subject allocation, and different exposures are assessed in a retrospective manner.
- Cross-sectional research evaluates both exposure and outcome concurrently.
- Each of these design methods possesses different strengths and weaknesses in answering research questions, as well as underlying many study subtypes.

International Council for Harmonization

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines
- ICH (Full form = International Conference on Harmonisation) is a committee that provides the pharmaceutical stability guidelines for industries. ICH stability guidelines for stability conditions and testing are followed throughout the world for product quality [1-5].

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- **A primary purpose of the ICH** is to: Minimize the need for redundant research. The ICH GCP Guidelines: Set standards for the design, conduct, monitoring and reporting of clinical research

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories:

- Q: Quality Guidelines.
- S: Safety Guidelines.
- E: Efficacy Guidelines.
- M : Multidisciplinary Guidelines

Good Clinical Practice (GCP)

- Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, and monitoring, auditing, recording, analyses and reporting of clinical trials. It also serves to protect the rights, integrity and confidentiality of trial subjects
- Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles

Clinical trials:

- Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people. Clinical research trials are sometimes lifesaving.

Schedule Y.

- Refers to requirements and guidelines to be followed in order to attain permission of: Importing and/or Manufacturing New Drugs to market or To undertake clinical trials in India [6-8].

Quality Guidelines

- Q1A - Q1F Stability
- Q1A(R2)- Stability Testing of New Drug Substances and Products
- Q1B Stability Testing : Photostability Testing of New Drug Substances and Products
- Q1C- Stability Testing for New Dosage Forms
- Q1D -Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- Q1E -Evaluation of Stability Data
- Q1F- Stability Data Package for Registration Applications in Climatic Zones III and IV
- Q2- Analytical Validation
- Q2(R1)- Validation of Analytical Procedures: Text and Methodology
- Q2(R2)/Q14 EWG -Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation
- Q3A - Q3D Impurities
- Q3A(R2)- Impurities in New Drug Substances
- Q3B(R2)- Impurities in New Drug Products
- Q3C(R6)- Maintenance of the Guideline for Residual Solvents
- Q3C(R8)- Maintenance EWG Maintenance of the Guideline for Residual Solvents
- Q3D(R1)- Guideline for Elemental Impurities
- Q3D(R2)- Maintenance EWG Revision of Q3D(R1) for cutaneous and transdermal products
- Q3D- Training Implementation of Guideline for Elemental Impurities
- Q3E- informal WG
- Impurity: Assessment and Control of Extractable and Leachable for Pharmaceuticals and Biologics
- Q4A - Q4B Pharmacopoeias
- Q4A- Pharmacopoeial Harmonisation
- Q4B- Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
- Q4B Annex 1(R1)- Residue on Ignition/Sulphated Ash General Chapter
- Q4B Annex 2(R1)- Test for Extractable Volume of Parental Preparations General Chapter
- Q4B Annex 3(R1) -Test for Particulate Contamination: Sub-Visible Particles General Chapter
- Q4B Annex 4A(R1)-Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter
- Q4B Annex 4B(R1)-Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms General Chapter
- Q4B Annex 4C(R1)-Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter
- Q4B Annex 5(R1)- Disintegration Test General Chapter
- Q4B Annex 6- Uniformity of Dosage Units General Chapter
- Q4B Annex 7(R2) -Dissolution Test General Chapter
- Q4B Annex 8(R1)- Sterility Test General Chapter
- Q4B Annex 9(R1) --Tablet Friability General Chapter
- Q4B Annex 10(R1) -Polyacrylamide Gel Electrophoresis General Chapter
- Q4B Annex 11 -Capillary Electrophoresis General Chapter
- Q4B Annex 12- Analytical Sieving General Chapter
- Q4B Annex 13 -Bulk Density and Tapped Density of Powders General Chapter
- Q4B Annex 14 -Bacterial Endotoxins Test General Chapter
- Q4B FAQs -Frequently Asked Question
- Q5A - Q5E -Quality of Biotechnological Products

- Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- Q5A(R2) EWG Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- Q5B Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- Q5C- Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- Q5D -Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
- Q5E- Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
- Q6A Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- Q6B Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- Q7- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- Q7 Q&As-Questions and Answers: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- Q8 -Pharmaceutical Development
- Q8(R2) -Pharmaceutical Development
- Q8/9/10 Q&As (R4) Q8/Q9/Q10 - Implementation
- Q9 -Quality Risk Management
- Q9-(R1) informal WG Quality Risk Management
- Q8/9/10 Q&As (R4) Q8/Q9/Q10 - Implementation
- Q10- Pharmaceutical Quality System
- Q11- Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
- Q11 Q&As Questions & Answers: Selection and Justification of Starting Materials for the Manufacture of Drug Substances
- Q12- Lifecycle Management
- Q12- Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- Q12- IWG Training on Regulatory and Technical Considerations for Pharmaceutical Product Lifecycle Management
- Q13 Continuous Manufacturing of Drug Substances and Drug Products
- Q14 -Analytical Procedure Development
- Q2(R2)/Q14 EWG Analytical Procedure Development and Revision of Q2 (R1) Analytical

Safety Guidelines

- S1A - S1C Carcinogenicity Studies
- S1A -Need for Carcinogenicity Studies of Pharmaceuticals
- S1B Testing for Carcinogenicity of Pharmaceuticals
- S1C(R2-) Dose Selection for Carcinogenicity Studies of Pharmaceuticals
- S1(R1)- EWG Rodent Carcinogenicity Studies for Human Pharmaceuticals
- S2 -Genotoxicity Studies
- S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- S3A - S3B Toxicokinetic and Pharmacokinetics
- S3A Note for Guidance on Toxicokinetic: The Assessment of Systemic Exposure in Toxicity Studies
- S3A Q&As Questions and Answers: Note for Guidance on Toxicokinetic: The Assessment of Systemic Exposure - Focus on Micro sampling
- S3B- Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
- S4 -Toxicity Testing
- S4 -Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)
- S5- Reproductive Toxicology
- S5(R2)- Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
- S5(R3) -EWG Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals
- S6- Biotechnological
- S6- Biotechnological Products
- S6(R1)- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- S7A - S7B Pharmacology Studies
- S7A- Safety Pharmacology Studies for Human Pharmaceuticals
- S7B The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals
- E14/S7B IWG Questions & Answers: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential
- S8- Immunotoxicology Studies
- S8- Immunotoxicity Studies for Human Pharmaceuticals
- S9- Nonclinical Evaluation for Anticancer Pharmaceuticals
- S9 Q&As Questions and Answers: Nonclinical Evaluation for Anticancer Pharmaceuticals
- S10-Photo safety Evaluation of Pharmaceuticals
- S11-Nonclinical Paediatric Safety
- S11 EWG Nonclinical Safety Testing in Support of Development of Paediatric Medicines

- S12-Non-clinical Biodistribution Studies for Gene Therapy Products

Efficacy guidelines

- E1- Clinical Safety for Drugs used in Long-Term Treatment
- E1- The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions
- E2A - E2F Pharmacovigilance
- E2A-Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2B(R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)
- E2B(R3) Q&As Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
- E2B(R3) EWG/IWG Electronic Transmission of Individual Case Safety Reports (ICSRs)
- E2C(R2) Periodic Benet-Risk Evaluation Report
- E2C(R2) Q&As Questions & Answers: Periodic Benet-Risk Evaluation Report E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D(R1) EWG Post Approval Safety Data Management: Definitions and Standards for Expedited Reporting
- E2E- Pharmacovigilance Planning
- E2F Development Safety Update Report
- E3-Clinical Study Reports
- E3 Structure and Content of Clinical Study Reports
- E3 Q&As (R1) Questions & Answers: Structure and Content of Clinical Study Reports
- E4-Dose-Response Information to Support Drug Registration
- E5-Ethnic Factors
- E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data
- E5 Q&As (R1) Questions & Answers: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6-Good Clinical Practice
- E6(R2) Good Clinical Practice (GCP)
- E6(R3) EWG Good Clinical Practice (GCP)
- E7-Clinical Trials in Geriatric Population
- E7 Studies in Support of Special Populations: Geriatrics
- E7 Q&As Questions & Answers: Studies in Support of Special Populations : Geriatrics
- E8-General Considerations for Clinical Trials
- E8(R1) EWG Revision on General Considerations for Clinical Studies
- E9-Statistical Principles for Clinical Trials
- E9(R1) EWG Addendum: Statistical Principles for Clinical Trials
- E10-Choice of Control Group and Related Issues in Clinical Trials
- E11 - E11A Clinical Trials in Paediatric Population
- E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Paediatric Population
- E11A EWG Paediatric Extrapolation
- E12-Clinical Evaluation by Therapeutic Category
- E12-Principles for Clinical Evaluation of New Antihypertensive Drugs
- E14 -Clinical Evaluation of QT E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
- E14Q&As(R3) Questions & Answers: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
- E14/S7B IWG-Questions & Answers: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential
- E15-Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
- E16-Qualification of Genomic Biomarkers
- E16-Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions
- E17-Multi-Regional Clinical Trials
- E17-General principles for planning and design of Multi-Regional Clinical Trials
- E18-Genomic Sampling and Management of Genomic Data
- E19-Safety Data Collection
- E19 EWG- Optimisation of Safety Data Collection
- E20-Adaptive Clinical Trials

Multidisciplinary Guidelines

- M1- MedDRA - Medical Dictionary for Regulatory Activities
- M1 PtC WG -MedDRA Points to Consider
- M2 -EWG Electronic Standards for the Transfer of Regulatory Information
- M3- Nonclinical Safety Studies
- M3(R2)- Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- M3(R2) Q&As (R2)- Questions & Answers: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- M4 -Common Technical Document
- M5- Data Elements and Standards for Drug Dictionaries
- M6- Gene Therapy

- M6- Virus and Gene Therapy Vector Shedding and Transmission
- M7- Mutagenic impurities
- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals
- M7(R1)- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- M7(R2) -Maintenance EWG/IWG Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- M8- Electronic Common Technical Document (eCTD)
- M8 eCTD v3.2.2 -Electronic Common Technical Document (eCTD) v3.2.2
- M8 eCTD v4.0- Electronic Common Technical Document (eCTD) v4.0
- M8 EWG/IWG -Electronic Common Technical Document (eCTD)
- M9- Biopharmaceutics Classification System-based Biowaivers
- M9 Q&As- on Biopharmaceutics Classification System-based Biowaivers
- M10 -Bioanalytical Method Validation
- M11 -Clinical electronic Structured Harmonised Protocol (CeSHarP)
- M12- Drug Interaction Studies
- M12 EWG -Drug Interaction Studies
- M13 -Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- M13- informal WG Bioequivalence for Immediate-Release Solid Oral Dosage Forms

(ICH-GCP)

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.
- The objective of this ICH GCP guidance is to provide a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- The guidance 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.
- This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.
- The principles established in this guidance may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

Important Principles of ICH GCP to Conduct Clinical Trial

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) Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3) The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4) The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5) Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6) A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7) The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8) Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9) Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10) All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11) The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12) Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol. Contains Nonbinding Recommendations
13) Systems with procedures that assure the quality of every aspect of the trial should be implemented [8-12].

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