DEPTH OF BIOLOGY

Unit - 1

Regulatory Perspectives of Clinical Trials:

Origin and Principles of International Conference on Harmonization - Good Clinical Practice (ICH-GCP) guidelines

Ethical Committee: Institutional Review Board, Ethical Guidelines for Biomedical Research and Human Participant-Schedule Y, ICMR

Informed Consent Process: Structure and content of an Informed Consent Process Ethical principles governing informed consent process

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Clinical Research & Pharmacovigilance-

Clinical trials = systematic studies in humans to test safety, efficacy, and quality of new drugs.

From a regulatory perspective, trials must follow strict laws, guidelines, and ethics to protect patients and generate reliable data.

Regulatory authorities (like USFDA, EMA, CDSCO, ICH) ensure trials are done properly.

Purpose of Regulation

To protect human participants (safety, rights, well-being).
To ensure scientific validity (data must be accurate, reliable, unbiased).
To make sure drugs reaching the market are safe and effective.

Regulatory Requirements in Clinical Trials

(A) Ethical Approval-

Every clinical trial must be approved by an Ethics Committee / Institutional Review Board (IRB).

Ensures respect for human rights and ethical standards.

Based on Declaration of Helsinki principles.

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(B) Guidelines and Standards-

ICH-GCP (International Conference on Harmonisation – Good Clinical Practice) is the gold standard.

GCP ensures:

Protection of trial subjects.

Proper conduct of studies.

High quality and reliable data.

(C) Regulatory Authority Permission

Sponsor must apply to the national drug regulatory authority before starting the trial.

Example:

USFDA in USA

EMA in Europe

CDSCO / DCGI in India

(D) Informed Consent

Every participant must give voluntary written consent after understanding risks, benefits, and purpose.

(E) Safety Monitoring-

Adverse events must be reported.

Data Safety Monitoring Board (DSMB) or Independent Ethics Committee reviews ongoing safety.

3. Phases of Clinical Trials (Regulatory View)-

Phase I → Safety, tolerability, dose (in healthy volunteers).

Phase II → Efficacy and safety in small patient group.

Phase III → Large patient group, comparison with existing treatment.

Phase IV → Post-marketing surveillance (long-term safety).

Regulators review each phase data before approving next step.

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4. International Guidelines and Framework

ICH (International Council for Harmonisation) → harmonized global guidelines (GCP, safety, quality).

WHO guidelines → for developing countries.

FDA, EMA, CDSCO → country-specific rules.

5. Practical Considerations in Regulatory Perspective

Transparency → Trials must be registered in public databases (like ClinicalTrials.gov, CTRI in India).

Documentation → Protocols, investigator brochures, informed consent forms must be submitted.

Inspection & Audit → Regulators may audit trial sites.

Patient Safety First → always the top priority.

International Conference on Harmonisation (ICH)

Origin of ICH-

Before 1990, each country (USA, Europe, Japan) had different drug regulations.
This caused duplication of studies, wasted time and money, and delayed patient access to new medicines.

To solve this, regulators and pharmaceutical industry representatives from USA, EU, and Japan came together in 1990 (Brussels, Belgium).

They formed the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

Aim: To harmonize (make uniform) drug regulations globally.

Principles of ICH-

The ICH works on some core principles:

(A) Harmonization

Create common technical guidelines for drug registration.

Avoid unnecessary duplication of tests across countries.

(B) Safety, Quality, Efficacy

Guidelines cover three main areas:

Quality (Q) → standards for manufacturing & stability.

Safety (S) → toxicology, pharmacology, and risk studies.

Efficacy (E) → clinical trial design and conduct.

Later, Multidisciplinary (M) topics were added (e.g., medical terminology, electronic submissions).

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(C) Scientific Consensus-
Experts from regulatory agencies and industry come together to draft guidelines.
Ensures guidelines are based on sound science and practicality.

(D) Transparency-
Draft guidelines are made public for comments before final approval.

(E) Global Acceptance-
Though started with US, EU, Japan → now guidelines are used worldwide (including WHO, India, Canada, China etc.).

(F) Patient Benefit-
Faster drug development → patients get safe, effective medicines earlier.
Avoids repetition of animal/human testing → more ethical.

ICH-GCP Guidelines

(International Council for Harmonisation – Good Clinical Practice)

Introduction-

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

GCP = Good Clinical Practice.

ICH-GCP provides ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials.

Purpose: To ensure safety, rights, and well-being of participants and credibility of clinical trial data.

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Objectives of ICH-GCP-

Protect the rights, safety, and well-being of human subjects.

Ensure reliable, accurate, and credible clinical trial data.

Provide a unified standard accepted internationally by regulatory authorities.

Facilitate mutual acceptance of trial data across countries.

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Principles of ICH-GCP-

Ethical Conduct – Clinical trials should follow ethical principles (Declaration of Helsinki).
Risk-Benefit Balance – Risks must be justified by potential benefits.
Rights and Safety First – Subject welfare > scientific interests.
Adequate Information – Trials should be based on preclinical and clinical evidence.
Scientific Soundness – Study protocols must be clear, justified, and scientifically valid.
Compliance with Protocol – Approved by Ethics Committee / IRB.
Qualified Investigators – Only trained, qualified professionals should conduct trials.
Informed Consent – Voluntary participation with full understanding.
Confidentiality – Protect privacy and data of subjects.
Data Integrity – Trials must be recorded, handled, and stored accurately.
Quality Assurance – Systems in place for monitoring, auditing, and compliance.

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Key Components-

Investigator Responsibilities: Ensure subject safety, follow protocol, obtain informed consent, report adverse events.

Sponsor Responsibilities: Provide financial and administrative support, select qualified investigators, ensure monitoring and auditing.

IRB / Ethics Committee: Approve and oversee ethical aspects of trial.

Trial Protocol: Detailed document describing objectives, design, methodology, and conduct of study.

Essential Documents: Protocols, consent forms, case report forms (CRFs), monitoring reports, final study reports.

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Benefits of ICH-GCP-

Ensures ethical standards in clinical trials.

Improves global acceptance of data (saves time, cost, and duplication).

Protects participants' rights and safety.

Ensures high quality and reliable data for regulatory approvals.

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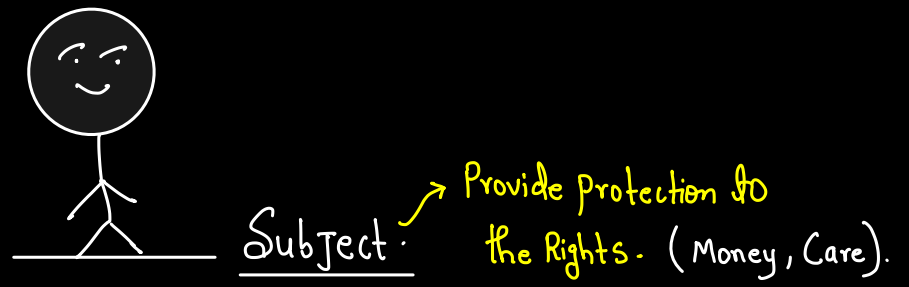
Institutional Review Board / Independent Ethics Committee (IRB/IEC)

- IRB/IEC- independent committee
- Consist of medical member, scientific member & non-scientific member
- They are responsible for providing protection to the rights for the subject [which they undergo clinical trials] by reviewing, approved & also provides updates in clinical trials



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Members of IRB/IEC [8-12 members]

- Chair person
- 1-2 person from life sector
- 1 legal advisor/ retired judge
- 1-2 clinicians from various institute
- 1 social scientist
- 1 philosopher
- 1 person from community
- 1 member secretry

RESPONSIBILITIES

To provide adequate care to human subjects [who undergo clinical trial]	To achieve international & regional acceptance of clinical trials	To provide sufficient payment to the subject

DOCUMENTS REVIEW BY THE IRB/IEC

- Research protocol
- Written consent form [for enroll in clinical trials]
- Subject selection procedure [advertisements]
- Written information provide to subject
- Investigational brochure
- Subject payment
- Investigator updated C.V.

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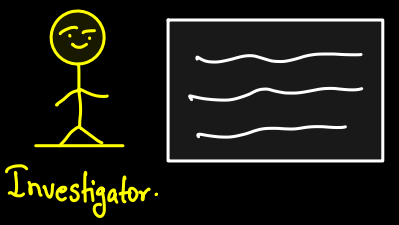
- PROCESS OF REVIEW

Investigator Submit Research Protocol



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It is review either it is complete or not/approvable or not accurate

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If research protocol is complete or approvable then it is review by IRB/IEC

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If all good then it is approvable & investigator received a written approval

If not → Investigator need correction

If not → Major mistake [disappointed/-ve]
Re-evaluated by investigator

↓

Clinical trial initiate

Ethical Guidelines for Biomedical Research

Introduction-

Biomedical research involves experiments on human participants, animals, or biological samples.

Since it deals with life, health, and dignity, strict ethical guidelines are required.

Aim: Protect safety, rights, and well-being of research participants while ensuring scientific validity.

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Basic Ethical Principles-

(Adopted from Belmont Report and Declaration of Helsinki)

Respect for Persons (Autonomy)

Informed consent must be taken.

Participants should voluntarily agree after understanding risks and benefits.

Beneficence

Research should maximize benefits and minimize possible harm.

Non-Maleficence

"Do no harm." Avoid unnecessary risks or suffering.

Justice

Fair selection of participants (no exploitation of vulnerable groups).

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Ethical Guidelines for Human Research-

Ethics Committee / Institutional Review Board (IRB): Must approve study protocols.

Informed Consent: Clear explanation of purpose, procedures, risks, benefits, and confidentiality.

Confidentiality: Protect privacy and personal data.

Risk-Benefit Assessment: Research should not expose subjects to disproportionate risk.

Special Protection: For vulnerable groups (children, pregnant women, mentally challenged, prisoners).

Compensation: For trial-related injury or death.

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Ethical Guidelines for Animal Research-

Replacement: Use alternatives (cell culture, computer models) wherever possible.

Reduction: Use the minimum number of animals needed for valid results.

Refinement: Modify procedures to reduce pain and suffering.

Ethical Clearance: Mandatory approval from Institutional Animal Ethics Committee (IAEC).

Follow CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) in India.

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International Ethical Codes-

Nuremberg Code (1947): First set of rules after WWII; stressed voluntary consent.

Declaration of Helsinki (1964, revised): Issued by WMA – cornerstone of medical ethics.

Belmont Report (1979): Laid down autonomy, beneficence, justice.

CIOMS Guidelines (WHO, 1993): Special focus on low-resource countries.

ICH-GCP (1996): Global standard for clinical trials.

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Importance of Ethical Guidelines-

Protect human dignity and rights.

Prevent exploitation of participants.

Improve scientific credibility of research.

Ensure public trust in biomedical research.

Schedule Y – Human Participants in Clinical Research (India)-

Introduction-

Schedule Y is part of the Drugs and Cosmetics Rules, 1945 (India).

Provides regulatory requirements for:

Clinical trials of new drugs in India.

Responsibilities of investigators, sponsors, and ethics committees.

Protection of human participants in research.

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Phases of Clinical Trials (as per Schedule Y)-

Phase I (Human/Clinical Pharmacology)
Conducted in healthy volunteers (20–80).
Objective: Study safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD).

Phase II (Therapeutic Exploratory)
Conducted in patients (100–300).
Objective: Preliminary efficacy and safety evaluation.

Phase III (Therapeutic Confirmatory)
Conducted in larger patient groups (500–3000).
Objective: Confirm efficacy, monitor adverse reactions, compare with standard therapy

Phase IV (Post-Marketing Surveillance)-

After drug approval.

Objective: Detect rare/long-term adverse effects, real-world safety.

Ethical Requirements for Human Participants (Schedule Y)-

1. Ethics Committee Approval-

Every trial must be approved by an Institutional Ethics Committee (IEC).
IEC ensures protection of rights, safety, and well-being of participants.

2. Informed Consent-

Written informed consent is mandatory.

Must include purpose, procedures, potential risks/benefits, confidentiality, voluntary participation.

For illiterate participants → witnessed consent required.

For minors or incapacitated persons → consent from legally acceptable representative (LAR).

3. Compensation and Medical Care

Sponsor must provide free medical care for any trial-related injury.

Compensation must be given in case of injury or death.

4. Vulnerable Populations

Extra precautions for children, pregnant women, prisoners, mentally challenged, poor/uneducated groups.

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Roles and Responsibilities-

Investigator:
Ensure protocol compliance.
Protect participants' rights and safety.
Report adverse events.

Sponsor:
Provide financial/administrative support.
Arrange for monitoring, auditing, and compensation.

Ethics Committee:
Independent body ensuring ethical conduct.
Review trial protocol, consent form, and safety reports.

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Importance of Schedule Y for Human Participants-

Ensures ethical and scientific conduct of trials in India.

Protects rights, safety, and well-being of participants.

Provides legal framework for clinical research.

Brings Indian clinical trial standards closer to international norms (ICH-GCP).

ICMR – Indian Council of Medical Research

ICMR = India's apex body for the formulation, coordination, and promotion of biomedical research.

Established in 1911 as the Indian Research Fund Association (IRFA); renamed ICMR in 1949.

Functions under the Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India.

Head office: New Delhi.

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Objectives of ICMR-

Promote, coordinate, and conduct biomedical research in India.

Formulate ethical guidelines for human and animal research.

Address public health issues (communicable and non-communicable diseases).

Develop new drugs, diagnostics, vaccines, and treatment strategies.

Provide training, fellowships, and research grants.

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ICMR Ethical Guidelines for Biomedical Research (2017 – latest update)

Core Ethical Principles

1. Respect for Persons (Autonomy) – Informed consent, voluntary participation.
2. Beneficence – Maximize possible benefits.
3. Non-Maleficence – Avoid causing harm.
4. Justice – Fair participant selection and distribution of benefits.
5. Confidentiality & Privacy – Protect participant data.
6. Accountability & Transparency – Researcher responsibility and reporting.

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Ethical Guidelines for Human Participants-

Informed Consent – written, audio-visual (for clinical trials), or witnessed.

Vulnerable Populations – special protection for children, pregnant women, mentally challenged, socio-economically disadvantaged.

Compensation – for research-related injury or death.

Ethics Committees (IEC/IRB) – all biomedical research must be reviewed and approved.

Community Engagement – when research involves public health or community-based studies.

Ethical Guidelines for Animal Research-

Follow the 3Rs principle:
Replacement – use alternatives instead of animals when possible.

Reduction – minimize the number of animals used.

Refinement – modify methods to minimize pain and distress.

Governed by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals).

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-Functions of ICMR

Conducts research through permanent institutes, centers, and field units across India (e.g., NIRRH, NIOH, NIV, NCDIR).
Provides funding and grants to universities, medical colleges, and NGOs.
Publishes research journals, guidelines, and policy documents.
Collaborates with WHO, NIH, and other international agencies.

-Importance of ICMR Guidelines

Ensure ethical and scientific validity of biomedical research in India.
Protect human dignity, rights, and safety.
Promote responsible animal use in research.
Improve public trust in biomedical science.
Help India align with international research standards (like ICH-GCP, CIOMS, Helsinki Declaration).

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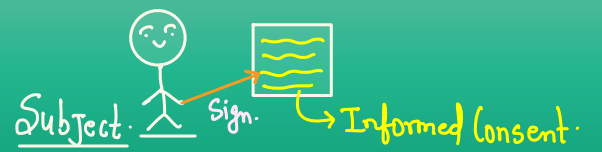
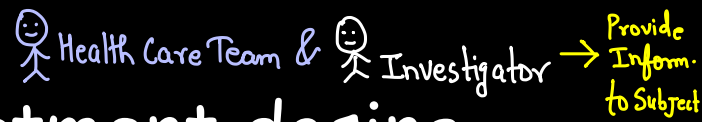


Education ⟵ **Informed consent** ⟶ Agreement

- It is a type of document/ form which is filled or signed by the subject before participating clinical trial
- Here we provide total information regarding trials to subject
- Health care team/ investigator provide all the information to human volunteer/subject who undergo clinical trials



- * Information like risk of trial, benefits of trial, treatment dosing frequency
- Subject also consult with team if they have any queries regarding clinical trials

* TYPES OF INFORMED CONSENT

A. Verbal consent- 1. investigator IRB approved *[must be from scientific background]* & 2. designees

B. Written consent

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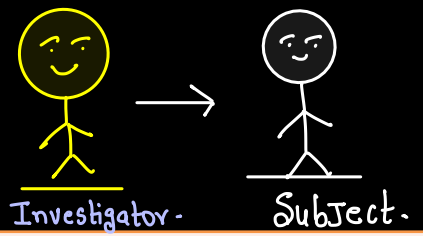
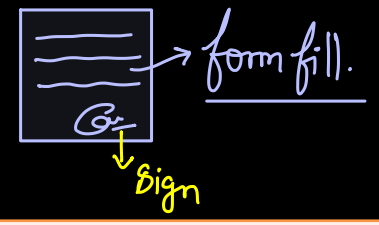
Designees- Person who is officially chosen to do something. No scientific background but they are experienced in trials





VERBAL CONSENT	WRITTEN CONSENT
1. Education- all the information related to trial are given to subject [either safety, toxicity] & also give opportunity to subject to share or solve his/her all query related to trial 2. Provide information sheet to subject –written document that has all information regarding trials. Give sufficient time to patients [hours-days] 3. Answer the queries [provide proper answer to subject 4. Verbal agreement taken by subject	1. Education- all the information related to trial are given to subject [either safety, toxicity] & also give opportunity to subject to share or solve his/her all query related to trial 2. Consent form filled by subject – has all information mentioned in form 3. Investigator & subject session 4. Written agreement subject sign*

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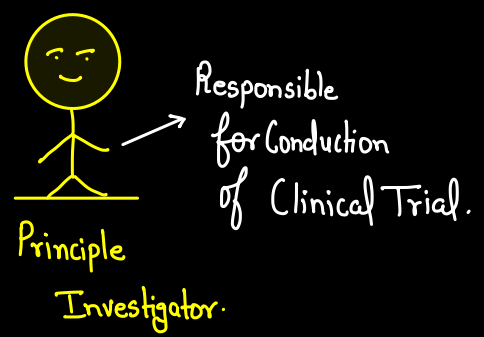
➢GCP OBLIGATION

- **GOOD CLINICAL PRACTICES** these are guidelines for conduction of clinical trials
- GCP aims to ensure that the studies are scientifically authentic & all the clinical property of investigational product are properly documented

Investigational Product.

❖GCP OBLIGATION FOR Investigators

- **INVESTIGATOR-** a person who is responsible for conduction of clinical trials at trial site [principal investigator]
- They are known as real heroes of clinical studies



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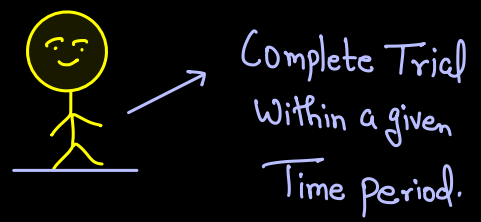
1. QUALIFICATION & EXPERIENCE- *[according to GCP guideline 4.1 of ICH]-*

- The P.I. must be qualified by education, training, experience for proper conduction of clinical studies

He/ she must obey the GCP guidelines

2. ADEQUATE RESOURCE - *[according to GCP guideline 4.2 of ICH]-*

- Required a number of suitable subjects within the agreed recruitment
- The investigator should have sufficient time to properly conduct & complete the trial within the agreed trial period



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3. MEDICAL CARE OF STUDY PARTICIPANTS OR TRIAL SUBJECTS - *[ICH GCP 4.3]*

- Investigator must provide appropriate medical care for both study related adverse event of drug & for all medical condition like fever, cough

4. COMMUNICATION WITH INSTITUTION REVIEW BOARD [IRB]-

- It provide approval for conduction of clinical trial
- Study may not begin prior to obtaining IRB approval
- Study of clinical trial are done under the guideline of IRB

5. COMPLIANCE WITH THE PROTOCOL- *[ICH GCP 4.5]*

- Investigator is responsible for ensuring that the study is

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Conducted in compliance / accordance with the research protocol for a better & successful clinical studies

6. USE OF INVESTIGATIONAL PRODUCT- *[ICH GCP 4.6]*

- If the study use investigational product then the P.I responsible for ensuring that the investigational product is used only in accordance with study protocol & federal regulation

7. RANDOMIZATION & BLINDING *[ICH GCP 4.7]-*

- The P.I is responsible for randomly picking/ choosing the subject & applying drug on subject without informing him/her

8. INFORMEDD CONSENT *[ICH GCP 4.8]*

- Helsinki declared ethical principle & we have to follow all the ethics during clinical trials

9. RECORDS & REPORTS *[ICH GCP 4.9]*

- P.I is responsible for maintaining all the clinical records & timely reported to the sponsor

10. PROGRESS REPORT *[ICH GCP 4.10]*

- The investigator should provide written report to sponsor

11. SAFETY REPORTING *[ICH GCP 4.11]*

- All adverse or serious event must be reported to sponsor

12. FINAL STUDY REPORT

- On completion of study the P.I is responsible for providing-

✓ All required reports to the sponsor & regulatory authorities

✓ A summary of study outcome to the I.R.B