DEPTH OF BIOLOGY

Unit- 2

Clinical Trials: Types and Design

Experimental Study- RCT and Non RCT,

Observation Study: Cohort, Case Control, Cross sectional Clinical Trial Study Team

Roles and responsibilities of Clinical Trial Personnel: Investigator, Study Coordinator, Sponsor, Contract Research Organization and its management

Pre - Clinical Trial.

STAGE 2

1. ANIMAL TRIAL- once you have the lead, you can check what a drug is actually doing in a living system, whether it is curing a disease , it is safe / efficient. All these parameters are checked in animal

- For successful conduction of animal trials we have to study certain
- Factors like pharmacokinetics & dynamics, toxicological
- This test are conducted to evaluate drug safety in two different animal species
- Animals are carefully monitored for side effects, after the study period the pathologist examine their organs for sign of toxicity
- Animals used in drug trials are [vertebrates] – cats, mice, frog & pigs etc

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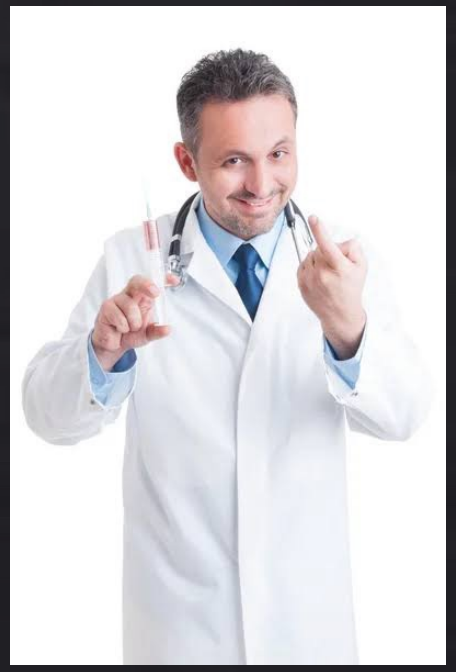

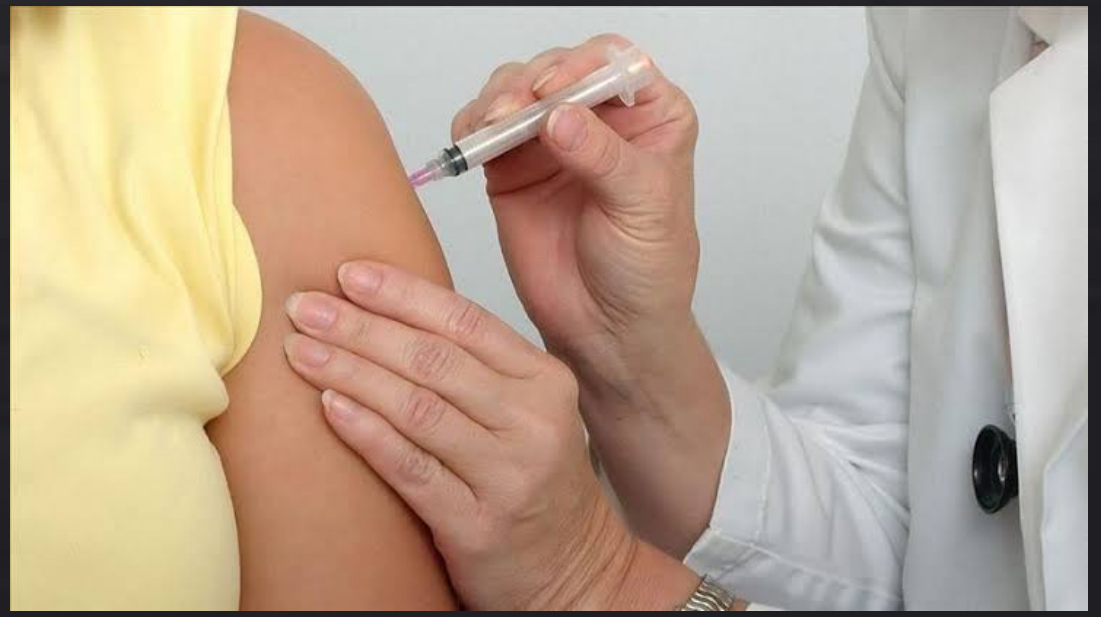

2. HUMAN TRIAL- also known as clinical trial, here we conduct long term toxicity study

- People of all ages can take part in clinical trials including children
- Clinical trials are done only after pre-clinical trials
- It provides evidence about safety & effectiveness of drug [check

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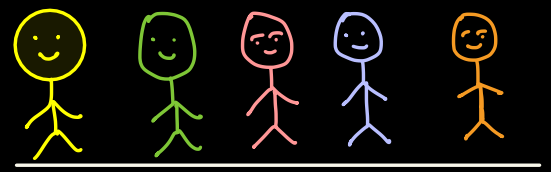
Potency, lethal effect , side effect & adverse effect]

- Clinical trials are research studies that explore whether a medical treatment or device is safe & effective for human

DIFFERENT PHASES IN CLINICAL TRIALS

A. PHASE 0- [micro dosing studies]



- Conducted on healthy volunteers [small number]
- This phase is conducted to know the pharmacokinetics [A,D,M,E] property of drug & to avoid costly phase I study for candidate Drug with unstable pharmacokinetics

B. PHASE I- [human pharmacology & safety phase]

→ To, Check Max. Tolerable Dose.

→ Check Safety of Drug.

- Conducted on healthy volunteers [20-100]

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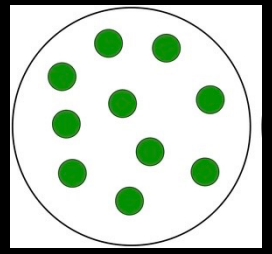
- This is performed to know the maximum tolerable dose or about the safety tolerability of drug, to check toxicity of drug



C. PHASE II- [therapeutic exploratory]

- Conducted on patient of homogeneous population [100-150]
- This is performed to know the therapeutic efficacy of drug , to know about dose/ dose ranging. & ceiling effect [approx. 33 % drugs passes this phase]

D. PHASE III- [therapeutic confirmatory]

- Conducted on heterogeneous population up to 5000 patient from several centers [check drug interaction, safety , efficacy]
- This is performed to confirm therapeutic efficacy & to establish the value of drugs in relationship to existing therapy [means compare the drug with existing marketed drug in order to check safety &

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efficacy-] & to check side effects of drug

E. PHASE IV- [post marketing surveillance] ⟶ Drug

- After phase III drug is approved by FDA and launched into market
- This is conducted on large number of patients being treated by practicing physician
- Purpose of this phase is to check rare [idiosyncrasy] & long term adverse effect
- Special group like children or pregnant women can be tested

- PRE CLINICAL DATA allow the researcher to estimate a safe starting dose of drug for clinical trials in human

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- Typically both in-vitro & in vivo test are performed, studies of drug toxicity include organs which are targeted by drug
- Three special types of toxicity performed- mutagenicity, carcinogenicity, teratogenicity

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Clinical Trials: Types and Design

Clinical Trial = A systematic study in human participants to evaluate the safety, efficacy, and dosage of new drugs, vaccines, devices, or treatment methods.

Follows ethical guidelines (ICMR, ICH-GCP, Schedule Y).

Conducted in phases (I–IV) to ensure safety and scientific validity.

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Types of Clinical Trials-

A. Based on Purpose

Treatment Trials – Test new drugs, combinations, or procedures.

Prevention Trials – Test vaccines, lifestyle modifications, preventive drugs.

Diagnostic Trials – Evaluate new tests/procedures for diagnosis.

Screening Trials – Detect diseases early.

Quality of Life (Supportive Care) Trials – Improve comfort in chronic illness.

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Based on Methodology

1. Randomized Controlled Trial (RCT)-
Gold standard; participants randomly assigned to groups (test vs control).

2. Non-Randomized Trials
Assignment not random → risk of bias.

3. Open-label Trial
Both researcher and participant know the treatment given.

4. Single-blind Trial
Participant doesn't know which treatment they are receiving.

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5. Double-blind Trial
Neither participant nor investigator knows → reduces bias.

6. Cross-over Trial
Participants receive both treatments (test and control) in sequence with a washout period.

7. Cluster Trial
Groups (schools, villages) rather than individuals are randomized.

8. Adaptive Trials
Trial design is modified as results emerge (flexible).

Meaning of Design in Clinical Trials

Design = The overall plan, structure, or strategy of how a clinical trial will be conducted.

It tells how participants will be selected, allocated, treated, monitored, and evaluated during the study.

A good design ensures that results are scientifically valid, reliable, and unbiased

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Key Elements of Clinical Trial Design-

Objective of the trial – What is being tested? (safety, efficacy, dose, prevention, diagnosis).
Study population – Who will be included (patients, healthy volunteers)?
Randomization – Method of assigning participants to groups.
Blinding – Whether participants/investigators know which treatment is given.
Control group – Standard drug, placebo, or no treatment for comparison.
Intervention – What treatment or procedure is being tested.
Endpoints/outcomes – What is measured (e.g., symptom relief, survival rate).
Duration – How long the trial will run.

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Example-

If researchers want to test a new diabetes drug:

They decide the design: a Randomized, Double-blind, Placebo-controlled trial.

Meaning: Patients are randomly assigned to new drug or placebo, neither patients nor doctors know which is given, and results are compared.

Experimental Studies – RCT & Non-RCT

Introduction-

Experimental studies = Research where the investigator intervenes (gives a drug, vaccine, or treatment) and observes the effect.

Unlike observational studies, here the researcher controls the exposure.

They are the gold standard for proving cause–effect relationships.

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Types of Experimental Studies-

Randomized Controlled Trials (RCTs)

Non-Randomized Controlled Trials (Non-RCTs)

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1. Randomized Controlled Trial (RCT)-

Definition: A study where participants are randomly assigned to either the experimental (treatment) group or the control (placebo/standard treatment) group.

Key Features

Randomization → Eliminates selection bias.

Control group → Provides comparison.

Blinding (single, double, triple) → Reduces observer and participant bias.

Statistical power → Large sample size improves validity.

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Steps in RCT-

-Formulate Hypothesis → Define objective clearly.

-Define Study Population → Inclusion & exclusion criteria.

-Randomization → Assign subjects randomly (lottery, computer software, random number tables).

-Blinding:

Single blind → Participant unaware.

Double blind → Participant + Investigator unaware.

Triple blind → Participant + Investigator + Data analyst unaware.

-Follow-up & Monitoring → Collect data on outcomes.

-Analysis → Compare results between groups using statistical methods.

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Advantages-

Gold standard for testing new drugs, vaccines, interventions.
Provides strongest evidence for causality.
Minimizes bias and confounding.

Disadvantages-

Expensive, time-consuming.
Requires large sample size.
Ethical concerns in withholding treatment/placebo.

2. Non-Randomized Controlled Trials (Non-RCTs)-

Definition-
Experimental study where participants are allocated to intervention/control groups without randomization.

Also called quasi-experimental studies.

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Steps in Non-RCT (Quasi-Experimental Study)-

-Formulate Research Question / Hypothesis

Define objective: e.g., "Does a new health education program reduce smoking rates?"

-Select Study Population

Choose participants or groups (patients, schools, communities).

No randomization - allocation depends on convenience, availability, or administrative decision.

-Divide into Groups

Intervention group → Receives the new treatment/program.

Control group → Receives standard care or no intervention.

Groups are not randomized, so baseline differences may exist.

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-Measure Baseline Data (Pre-Test)

Collect information before intervention (e.g., smoking rate, BP level, disease incidence).

-Apply Intervention

Provide the experimental treatment, vaccine, program, or health service to the intervention group.

-Follow-Up / Monitoring

Observe both groups over a defined period.

Ensure data collection on relevant outcomes.

-Measure Outcomes (Post-Test)

Collect data after intervention (e.g., reduced smoking, improved BP control).

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-Compare Results

Compare before vs after (within the intervention group).

Compare intervention vs control group.

Adjust for confounders if possible (since groups are not randomized).

-Interpretation

Evaluate whether observed effects are likely due to intervention or due to bias/ confounding factors.

-Report Findings

Present strengths, limitations, and recommendations.

Clearly acknowledge that evidence is weaker than RCT due to lack of randomization.

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Types of Non-RCT Designs-

Non-equivalent Control Group Design → Groups selected based on convenience, not random.

Before-After (Pre-Post) Study → Measure outcome in same group before and after intervention.

Time Series Analysis → Repeated measurements taken over time before and after intervention.

Community Trials → Entire communities (not individuals) receive intervention without randomization.

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Advantages of Non-RCT-

Easier, quicker, cheaper.
Useful when randomization is impractical or unethical.
Can still provide practical insights into interventions.

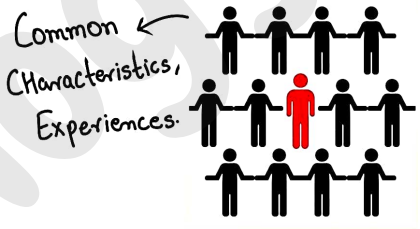
Limitations of Non-RCT-

High risk of bias (selection bias, confounding).
Causal relationship less reliable compared to RCT.
External factors may influence outcome.
Provides weaker scientific evidence.

Cohort studies

Cohort:

A group of people sharing common characteristics, experiences, or exposures, tracked over time to examine trends, outcomes, or effects.



Simple Examples:

1. A group of students graduating in 2020.
2. People born in 1990.
3. Employees hired in 2015.
4. Patients diagnosed with a specific disease.
5. Participants in a clinical trial.

Key Features:

1. Shared characteristics or experiences
2. Defined time period or exposure
3. Tracked over time

Types of Cohorts:

1. Age cohort (people born in the same year/period)
2. Exposure cohort (people exposed to a specific substance/event)
3. Disease cohort (people with a specific condition)
4. Occupational cohort (people in the same profession)

A cohort study is a type of research design used to investigate the causes and consequences (effect) of diseases, conditions, or outcomes by tracking a group of people (cohort) over time.

Types of cohort studies:

1. Prospective cohort study: Follows participants forward in time from exposure to outcome.
2. Retrospective cohort study: Looks back in time, examining past exposures and outcomes.
3. Combination →

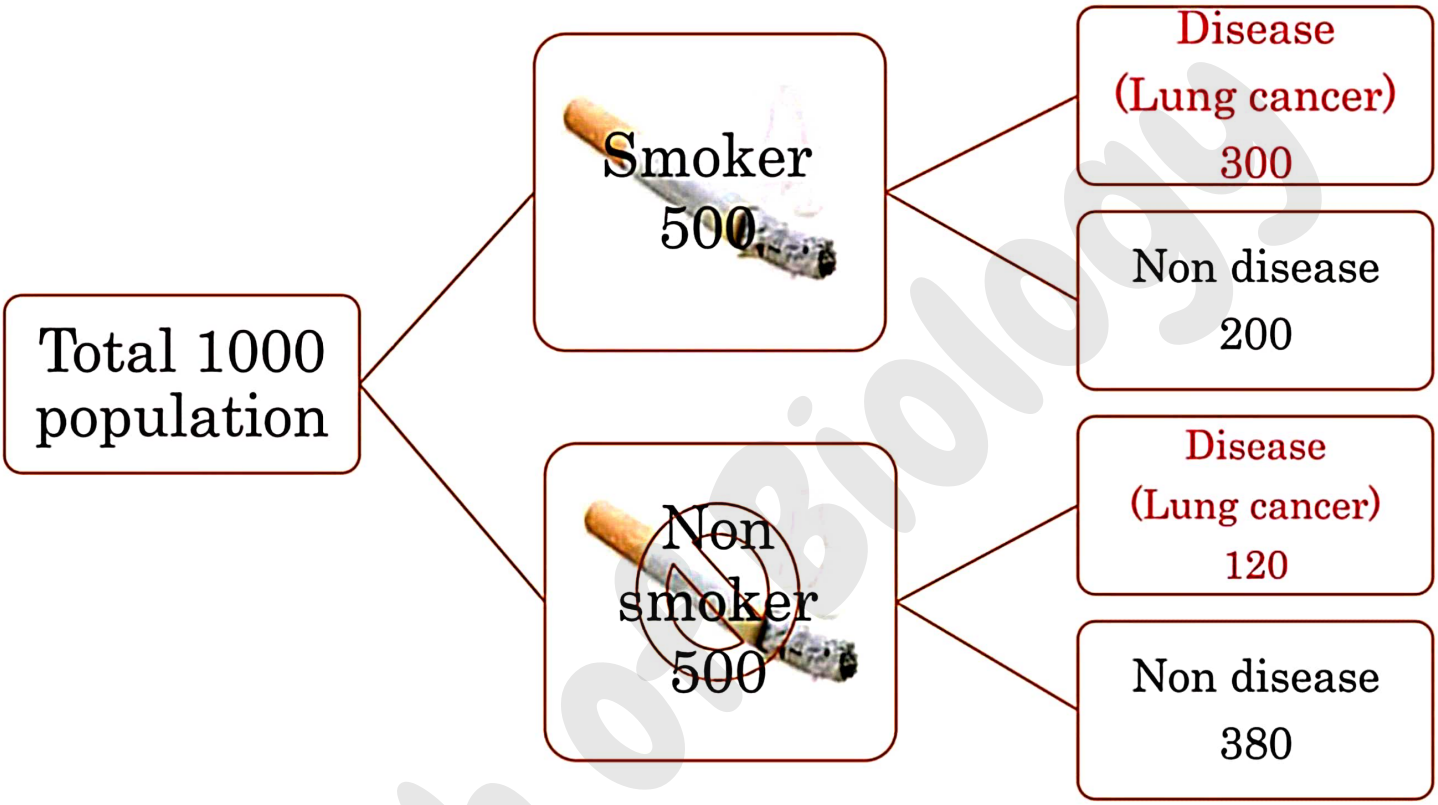
Advantages: →

1. Establishes cause-and-effect relationships
2. Identifies risk factors and associations
3. Provides incidence rates and disease progression information
4. Informs prevention and intervention strategies

Common applications:

1. Epidemiology
2. Public health research
3. Clinical research
4. Health services research

EXAMPLE



Disadvantages of Cohort Studies:

1. Time-consuming and resource-intensive
2. Expensive due to prolonged data collection and follow-up
3. Loss to follow-up and potential biases

Observational Studies

INTRODUCTION

- **Definition**: The population is observed without any interference by the investigator.
- A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given).

WHY OBSERVATIONAL STUDIES

- Cheaper
- Can examine long term effect
- Hypothesis generation
- Sometime, experimental study are not ethical

Observation Structures: **Types of Observational Studies**

1. Naturalistic Observation: Occurs in a natural, real-world setting without any manipulation or intervention.
2. Controlled Observation: Takes place in a controlled environment, such as a laboratory, where variables can be manipulated.

Observation Methods:

1. Structured Observation: Uses a predetermined framework or checklist to record observations.
2. Unstructured Observation: Involves open-ended observations without a predetermined framework.

Participation:

1. Participant Observation: The observer actively participates in the setting or activity being observed. ✓ (Smoke)
2. Non-Participant Observation: The observer does not participate in the setting or activity being observed. ✗ (Smoke)

Direct and Indirect Observation:

1. Direct Observation: The observer directly witnesses and records the behavior or phenomenon.
2. Indirect Observation: The observer uses secondary sources, such as reports or records, to gather data.

Advantages of Observational Study:

1. *Real-world insights*: Reflects natural experiences and outcomes.
2. *Cost-effective*: Less expensive than experimental designs.
3. *Long-term perspective*: Provides insights into disease progression.

Disadvantages of Observational Study:

1. *Lack of control*: Extraneous variables may influence outcomes.
2. *Confounding variables*: Unaccounted factors may affect results.
3. *Difficulty establishing causality*: Hard to determine cause-and-effect relationships.

1. Cross-Sectional Study (Observational Design)-

Definition

A cross-sectional study is an observational study in which data on exposure and outcome are collected at the same time (a "snapshot").

Key Features

No intervention (not a trial).

Useful to measure prevalence of disease or risk factor.

Quick, inexpensive.

Cannot establish cause-effect (temporality missing).

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Steps-

Define study objective.

Select study population (sample).

Collect data on exposure (risk factor) and outcome (disease).

Analyze association (e.g., smoking vs lung disease at a given time).

Report prevalence and correlations.

Clinical Trial Study Team-

In contrast, a clinical trial (experimental design) requires a multidisciplinary team.

Core Members

1. Principal Investigator (PI)

Leads the trial, responsible for scientific and ethical conduct.

2. Co-Investigators / Sub-Investigators

Assist PI in clinical and research tasks.

3. Study Coordinator / Research Nurse

Day-to-day management, participant recruitment, data collection.

4.Ethics Committee / Institutional Review Board (IRB)

Independent body ensuring safety, rights, and ethics.

5. Sponsor-

Provides funding, resources, and monitors compliance.

6. Data Safety Monitoring Board (DSMB)

Independent experts monitoring participant safety and trial integrity.

7. Pharmacists

Manage investigational drug storage, dispensing, accountability.

8. Biostatistician / Data Manager

Designs randomization, analyzes results, ensures data quality.

9. Regulatory Affairs Specialist

Ensures compliance with national/international guidelines (Schedule Y, ICH-GCP).

10. Clinical Research Associates (CRA)

Monitor trial sites, verify data, ensure protocol compliance.

Roles and responsibilities of Clinical Trial Personnel

1. Role of Investigators in Clinical Trials-

An investigator is a medically qualified person (usually a doctor) responsible for the conduct of a clinical trial at a particular site.

The Principal Investigator (PI) has overall responsibility, while sub-investigators assist.

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1. Protection of Participants-

The investigator must ensure the safety, rights, and well-being of all trial subjects.
Must avoid unnecessary risks and provide medical care whenever needed.
Patient safety is always more important than scientific results.

2. Compliance with Protocol, GCP, and Regulations-

The trial must be done exactly as per the approved protocol.
Must follow ICH-GCP guidelines and local laws (e.g., Schedule Y in India).
Any protocol changes must be approved by the ethics committee before implementation.

3. Informed Consent-

The investigator is responsible for taking written informed consent from every participant before enrolling.

Must explain:
Purpose of the study
Risks and possible side effects
Expected benefits
Rights of the participant (like the right to withdraw anytime)
Information should be given in simple language the participant can understand.

DEPTH OF BIOLOGY

4. Supervision and Delegation-

The PI is in charge of the entire study team at the site.

Tasks can be delegated (to sub-investigators, CRC, nurses, etc.), but final responsibility remains with PI.

Ensure all staff are qualified and trained for their tasks.

5. Safety Monitoring-

Continuously monitor the health of participants.

Record and report all Adverse Events (AEs) and Serious Adverse Events (SAEs) promptly to the sponsor and ethics committee.

Provide appropriate treatment or emergency care to participants if needed.

6. Accurate Data and Record Keeping-

Collect and maintain complete, correct, and timely data in Case Report Forms (CRFs).
Keep original source documents (lab reports, hospital records, test results).
Make trial data available for monitoring, audit, or inspection.

7. Investigational Product Accountability-

Ensure proper storage conditions of the study drug (temperature, security, etc.).
Keep detailed records of drug received, dispensed, returned, or destroyed.
Prevent misuse or unauthorized access to the drug.

8. Communication with Ethics Committee and Sponsor-

Submit the trial for ethics committee approval before starting.
Inform the committee about any amendments, safety issues, or progress reports.
Maintain good communication with the sponsor, monitor (CRA), and regulatory authorities.

9. Ethical and Scientific Integrity-

Conduct the trial with honesty and transparency.
Do not manipulate or falsify data.
Publish or report results truthfully, whether positive or negative.

2. Study Coordinator (CRC) – Roles and Responsibilities-

The Study Coordinator works under the supervision of the Principal Investigator (PI) and is the key person managing the day-to-day activities of a clinical trial at the site.

1. Participant Management-

Helps in recruitment and screening of participants.

Schedules study visits, follow-ups, and reminders.

Assists in obtaining informed consent and answering participant queries.

Ensures subjects follow the trial requirements (visit schedule, tests, medicines).

DEPTH OF BIOLOGY

2. Data Collection and Documentation-

Completes Case Report Forms (CRFs) and maintains source documents.
Ensures data is accurate, complete, and timely.
Assists with electronic data entry and query resolution.

3. Coordination and Communication-

Acts as a bridge between PI, sponsor, monitor (CRA), ethics committee, and participants.
Arranges site visits for CRA (monitoring visits).
Communicates trial updates and issues to the PI.

4. Investigational Product (IP) Handling-

Assists in receiving, storing, dispensing, and returning the investigational drug under PI's supervision.
Maintains drug accountability logs.

DEPTH OF BIOLOGY

5. Regulatory and Ethics Support-

Helps prepare documents for Ethics Committee submission.
Maintains regulatory binders and essential documents (protocols, approvals, consent forms, logs).
Ensures compliance with GCP and protocol.

6. Trial Logistics-

Organizes study supplies, kits, and lab samples.
Coordinates with laboratories for testing and shipment.
Keeps track of study materials and expiry dates.

3. Sponsor – Roles and Responsibilities in Clinical Trials-

A Sponsor is an individual, company, institution, or organization that initiates, manages, and finances a clinical trial.

The sponsor does not actually conduct the trial (that is the Investigator's role) but is responsible for planning, support, and oversight.

1. Trial Design and Planning-

Prepare the clinical trial protocol and study plan.
Select proper study design (e.g., RCT, crossover, etc.).
Provide investigator's brochure (drug information for investigators).
Ensure trial is scientifically sound and ethically acceptable.

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2. Investigator Selection-

Choose qualified investigators and sites with proper facilities.
Verify investigator's experience and training.
Provide protocol training to study staff.

3. Funding and Resource Support
Provide financial support for trial activities.
Supply investigational product (IP), study materials, and lab kits.
Ensure proper insurance/compensation for trial-related injuries.

4. Regulatory Responsibilities-

Submit trial applications to regulatory authorities (e.g., DCGI, FDA).
Obtain approvals from ethics committees before initiation.
Ensure compliance with ICH-GCP, Schedule Y, and local laws.

5. Safety Monitoring-

Collect and evaluate Adverse Event (AE) and Serious Adverse Event (SAE) reports.
Conduct ongoing safety assessments.
Take decisions about protocol modifications, dose changes, or trial termination if safety r
arise.

6. Monitoring and Quality Control-

Appoint Clinical Research Associates (CRAs) to monitor sites.
Ensure trials are conducted according to protocol and GCP.
Perform audits and inspections of trial sites.

7. Data Management and Statistics-

Provide systems for data collection and storage (CRFs, EDC systems).
Ensure data accuracy, confidentiality, and integrity.
Perform statistical analysis and prepare the final clinical study report.

8. Reporting and Publication-

Submit progress reports and safety reports to regulators and ethics committees.
Submit clinical trial results (positive or negative).
Apply for marketing authorization if results support drug approval.
Publish trial outcomes transparently.

Contract Research Organization (CRO) and Its Management

A Contract Research Organization (CRO) is a company, institution, or organization that provides clinical trial–related services to the pharmaceutical, biotechnology, and medical device industries on a contract basis.

The sponsor of the trial may transfer some or all of its duties to a CRO, but the ultimate responsibility for the trial always remains with the sponsor.

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Roles of CRO-

1. Clinical Trial Management
Assist in planning, initiation, conduct, monitoring, and closure of trials.
Help in patient recruitment and site selection.

2. Regulatory Support
Prepare and submit applications to regulatory authorities and ethics committees.
Ensure compliance with ICH-GCP and local regulations.

3. Data Management and Biostatistics
Design case report forms (CRFs).
Collect, validate, and analyze trial data.

4. Monitoring and Quality Assurance
Provide trained Clinical Research Associates (CRAs) to monitor sites.
Conduct audits and ensure protocol compliance.

DEPTH OF BIOLOGY

5. Pharmacovigilance-

Collect and evaluate adverse event reports.
Submit safety reports to sponsors and regulators.

6. Medical Writing-

Prepare trial documents such as study protocols, informed consent forms, clinical study reports, and publications.

7. Project Management-

Coordinate between sponsor, investigators, laboratories, and regulatory bodies.
Manage study timelines and budgets.

Management of CRO

For effective functioning, a CRO must have a proper management system.

1. Organizational Structure – clear roles (project managers, CRAs, data managers, statisticians, QA team).

2. Project Management – every trial is handled by a Project Manager who ensures timelines and resources.

3. Quality Management – implementation of Standard Operating Procedures (SOPs), audits, and inspections.

4. Regulatory Compliance – CRO must strictly follow ICH-GCP guidelines and country-specific regulations.

DEPTH OF BIOLOGY

5. Communication – regular reporting and coordination with sponsor, investigator sites, and authorities.

6. Training and Human Resources – all staff must be well-trained in GCP and trial procedures.

7. Financial Management – contracts, payments, and budgets must be transparent and properly handled.