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BP804ET**PHARMACEUTICAL REGULATORY SCIENCE**

B.Pharm 8th Semester

UNIT - IV
CLINICAL TRIALS**SYLLABUS COVERAGE — UNIT IV****Topics: Clinical trials**

Developing clinical trial protocols, Institutional Review Board / Independent Ethics committee – formation and working procedures, Informed consent process and procedures, GCP obligations of Investigators, sponsors & Monitors, Managing and Monitoring clinical trials, Pharmacovigilance – safety monitoring in clinical trials.

Introduction to Clinical Trials

A clinical trial is a systematic, prospective biomedical or behavioral research study involving human subjects, designed to answer specific questions about the safety, efficacy, pharmacokinetics, or pharmacodynamics of a drug, biologic, device, or intervention. Clinical trials form the bedrock of evidence-based medicine and are essential for bringing new medicines from the laboratory to patients.

Clinical trials are governed by national regulations (Indian NDCT Rules 2019, US 21 CFR Parts 50/56/312, EU Directive 2001/20/EC) and international ethical standards (Declaration of Helsinki, ICH E6 GCP, Belmont Report).

Feature	Details
Definition	A clinical trial is any study on human subjects intended to discover or verify the clinical, pharmacological, or pharmacodynamic effects of an investigational product
Purpose	Evaluate safety, efficacy, dose-response, pharmacokinetics, pharmacodynamics, and quality of life outcomes
Phases	Phase 0 (micro-dose) → Phase I (safety/PK) → Phase II (POC/dose-finding) → Phase III (pivotal) → Phase IV (post-marketing)
Governing Principles	Declaration of Helsinki (1964, revised 2013), ICH E6(R2) GCP, Belmont Report (1979), CIOMS Guidelines
Stakeholders	Sponsor, Investigator, CRO (Contract Research Organization), IRB/IEC, Subject/Patient, Monitor, Regulator
In India	NDCT Rules 2019 (New Drugs and Clinical Trials Rules); Schedule Y of D&C Rules (legacy); CDSCO oversight; Ethics Committee registration mandatory

Developing Clinical Trial Protocols

A clinical trial protocol is a formal, precisely written document that describes the objectives, design, methodology, statistical considerations, and organization of a clinical trial. It serves as the blueprint for the entire study — ensuring consistency, scientific rigor, patient safety, and regulatory compliance. The protocol is developed by the sponsor in consultation with investigators, statisticians, and regulatory advisors.

The protocol is the single most important document in a clinical trial. Every deviation from the protocol must be documented and justified. Protocol amendments require IRB/IEC approval before implementation.

Purpose of a Clinical Trial Protocol

- Define the scientific rationale and objectives of the study
- Standardize all study procedures across multiple sites (multi-center trials)
- Establish eligibility criteria to ensure appropriate subject selection
- Specify safety monitoring and stopping rules to protect subjects
- Provide the basis for IRB/IEC review and regulatory approval

- Serve as the reference document for audit and inspection
- Facilitate data integrity and reproducibility of results

Essential Elements of a Clinical Trial Protocol (ICH E6 R2)

As per ICH E6(R2) Good Clinical Practice, a clinical trial protocol must contain the following essential elements:

SECTION 1 — GENERAL INFORMATION

- Protocol title, protocol number, version number, and date
- Name and address of sponsor and sponsor's medical expert
- Name and title of the investigator(s) responsible for conducting the trial
- Name and address of the clinical laboratory(ies) and other medical/technical department(s)

SECTION 2 — BACKGROUND INFORMATION

- Name and description of the investigational product (IP)
- Summary of findings from non-clinical studies that have potential clinical significance
- Summary of known and potential risks and benefits, if any, to human subjects
- Description of route of administration, dosage, dosage regimen, and treatment period
- Statement that the trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements
- Description of the population to be studied
- References to literature and data relevant to the trial and providing background for the trial

SECTION 3 — TRIAL OBJECTIVES AND PURPOSE

- **Primary Objective:** The main question the trial is designed to answer (e.g., 'To demonstrate superior efficacy of Drug X vs. placebo in reducing HbA1c by $\geq 1\%$ at 24 weeks in T2DM patients')
- **Secondary Objectives:** Additional questions of interest (e.g., safety, quality of life, PK, PD)
- **Exploratory Objectives:** Hypothesis-generating; not pre-specified primary endpoints
- **Primary Endpoint:** The specific measurement corresponding to primary objective (e.g., HbA1c reduction from baseline at Week 24)
- **Secondary Endpoints:** Measurements for secondary objectives

SECTION 4 — TRIAL DESIGN

Design Element	Description / Options
Study Type	Interventional (participant receives experimental treatment) vs. Observational
Phase	Phase I, II, IIa, IIb, III, IIIb, or IV — defines purpose and scale

Randomization	Allocation of subjects to treatment by chance; prevents selection bias; methods: simple, block, stratified, adaptive
Blinding/Masking	Open-label, single-blind (subject masked), double-blind (subject + investigator), triple-blind (+ statistician/sponsor)
Control Type	Placebo-controlled, active-controlled, dose-response, historical control, no-treatment control
Design Type	Parallel group, crossover (with washout), factorial (multiple interventions), adaptive (protocol modifications based on interim data)
Multi-center	Multiple sites conducting same protocol simultaneously; increases enrollment speed and generalizability
Superiority/Non-inferiority/Equivalence	Defines the type of comparison: is new drug better than, as good as, or equivalent to comparator?

SECTION 5 — SUBJECT SELECTION (Inclusion/Exclusion Criteria)

Inclusion Criteria

- Define the minimum requirements a subject must meet to be eligible for the trial
- Examples: Age range (18-65 years), diagnosis of target disease (confirmed by specific criteria), adequate organ function (liver/kidney), written informed consent obtained
- Must be specific enough to ensure a homogeneous study population while allowing adequate enrollment

Exclusion Criteria

- Define conditions that disqualify a subject from enrollment even if inclusion criteria are met
- Examples: Pregnancy or lactation, concurrent serious medical condition, prior treatment with similar drug class, known hypersensitivity to IP, current substance abuse, participation in another clinical trial within 30 days
- Withdrawal Criteria: Conditions under which a subject is removed from the trial (protocol deviation, adverse event, withdrawal of consent, pregnancy)

SECTION 6 — TREATMENT OF SUBJECTS

- Investigational Product (IP): Name, pharmaceutical form, dose, dosing regimen, route of administration
- Dose escalation rules (Phase I): Starting dose, escalation scheme (e.g., modified Fibonacci), dose-limiting toxicity (DLT) criteria, MTD definition
- Treatment duration: Total treatment period; washout period (for crossover); follow-up period after treatment
- Permitted and prohibited concomitant medications and treatments
- IP accountability: Dispensing, storage, handling, reconciliation procedures
- Compliance monitoring: Pill counts, diaries, electronic monitoring, drug level measurements

SECTION 7 — ASSESSMENTS (Efficacy, Safety, PK/PD)

- Efficacy assessments: Instruments, questionnaires, laboratory tests, imaging assessments at each visit; scheduled time points (Schedule of Events/SoE table)
- Safety assessments: Adverse Event (AE) monitoring, vital signs, physical examination, laboratory safety panels (CBC, LFT, RFT, urinalysis), ECG
- Pharmacokinetic (PK) sampling: Blood/urine samples at pre-specified time points; sparse vs. intensive sampling
- Pharmacodynamic (PD) assessments: Biomarkers, functional assessments
- Schedule of Events (SoE) Table: Complete matrix of all assessments by visit; essential for site staff

SECTION 8 — STATISTICS

- Sample size calculation: Based on primary endpoint effect size, power (typically 80-90%), significance level ($\alpha = 0.05$), expected dropout rate
- Statistical analysis plan (SAP): Pre-specified; developed before database lock; analysis populations: Intent-to-Treat (ITT), Per Protocol (PP), Safety
- Primary analysis: Hypothesis test for primary endpoint
- Handling of missing data: Multiple imputation, LOCF (Last Observation Carried Forward), mixed models for repeated measures (MMRM)
- Interim analysis: Pre-specified rules; independent Data Safety Monitoring Board (DSMB) review
- Subgroup analyses: Pre-specified; exploratory only unless pre-specified as primary

SECTION 9 — DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

- Sponsor, regulatory authority, and IRB/IEC representatives have the right to audit, inspect, and monitor the trial
- Investigator must maintain source documents and allow direct access to monitor, auditor, regulatory inspector
- Source data: Original records (case records, lab reports, hospital records, subject diaries, electronic records)

SECTION 10 — ETHICS, ADVERSE EVENTS, AND MISCELLANEOUS

- Ethical conduct: Declaration of Helsinki, ICH E6 GCP, NDCT Rules 2019; IEC approval required before enrollment
- Adverse Event Reporting: SAE reporting timelines (7 days for fatal/life-threatening; 15 days for other serious); IEC and regulatory authority notification
- Data Handling and Record Keeping: CRF completion, data management, database lock, archiving (15 years minimum per ICH E6)
- Financing and Insurance: Financial arrangements, subject insurance/compensation for trial-related injury
- Publication Policy: Authorship, publication rights, disclosure of conflicts of interest

- Protocol deviations: Definition, documentation, CAPA (Corrective and Preventive Action) process

Protocol Amendments

- **Definition:** Any change to a protocol after it has received IEC/IRB and regulatory approval
- **Substantial Amendment:** Changes likely to impact the safety/rights of subjects or scientific value of the trial; requires IEC/IRB approval and regulatory authority notification BEFORE implementation
- **Non-Substantial Amendment:** Minor changes (clerical, typographical); notified to IEC/IRB but no prior approval needed
- **Emergency Protocol Deviation:** Change made to protect subject safety without prior approval; must be reported to IEC/IRB, sponsor, and regulatory authority as soon as possible
- **Documentation:** All amendments: version number, date, clear description of change and rationale

ICH E8(R1): The ICH E8(R1) guideline on 'General Considerations for Clinical Studies' (2021) emphasizes quality-by-design (QbD) principles in clinical trial protocol design, focusing on factors critical to the quality of trial results.

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

An Institutional Review Board (IRB) — called Independent Ethics Committee (IEC) in many countries — is an independent body constituted to review, approve, and provide ongoing oversight of clinical trials involving human subjects. Its primary mandate is to protect the rights, safety, dignity, and well-being of research participants.

No clinical trial may be initiated in India without approval from a duly registered Ethics Committee (EC) under the New Drugs and Clinical Trials Rules, 2019. The EC must be registered with CDSCO.

Regulatory Basis for IRB/IEC

Regulation / Guideline	Provision
Declaration of Helsinki (2013)	Article 23: Research must be approved by an independent ethics committee; Article 26: each potential subject must give informed consent
ICH E6(R2) GCP — Section 3	Defines IRB/IEC composition, functions, procedures, records; requires written operating procedures (SOPs)
NDCT Rules 2019 (India)	Rules 8-12: Ethics Committee registration, composition, functions, responsibilities; registration with CDSCO mandatory
21 CFR Part 56 (USA)	IRB regulations: composition, functions, review procedures, record-keeping requirements
EU Clinical Trials Regulation 536/2014	Ethics committee review as part of the combined regulatory-ethics assessment process; national-level competent authority
ICMR National Ethical Guidelines (2017)	Comprehensive guidelines for ethics committees in India; covers composition, quorum, conflict of interest, appeals

Formation / Composition of IRB/IEC

As per ICH E6(R2) Section 3.2 and NDCT Rules 2019 (Rule 8), the Ethics Committee must have the following composition:

Member Category	Qualification / Requirement	Minimum Number
Chairperson	Preferably from outside the institution; eminent in medical/scientific/social field; should not be from the institution where most research is conducted	1
Medical / Scientific Members	Physicians, pharmacologists, scientists with expertise in relevant research areas; assess scientific merit of research	At least 2-3
Non-scientific Member	Lay person (not from healthcare field); represents community perspective; often lawyer, social worker, or community representative	At least 1

Legal Expert	LLB or equivalent; advises on legal/regulatory matters related to clinical research	At least 1
Independent Member	Not affiliated with the institution or sponsor; ensures independence and avoidance of conflicts of interest	At least 1
Social Scientist / Psychologist	For social/behavioral research; assesses psychosocial risks to participants	As needed
Patient Advocate / NGO Representative	Represents patient perspective; provides community viewpoint	Recommended
Member Secretary	Manages EC administration, documentation, scheduling; often a trained research professional	1

Quorum: A quorum of at least 5 members (including Chairperson, one non-scientific member, one independent member, one medical member) must be present for valid decision-making. Decisions are taken by majority vote; the Chairperson has a casting vote.

Functions of the IRB/IEC

The primary function of the IRB/IEC is to ensure that clinical research is conducted ethically, protecting the rights, safety, dignity, and well-being of research participants. Specific functions include:

Initial Review

- Review and approve/disapprove the clinical trial protocol before study initiation
- Evaluate the scientific design and relevance of the study
- Assess the risk-benefit ratio for research participants
- Review the Informed Consent Form (ICF) and all participant-facing materials
- Evaluate Investigator's Brochure (IB) for pre-clinical and clinical safety data
- Review Investigator's qualifications and facilities at the trial site
- Assess adequacy of participant insurance/compensation in case of trial-related injury
- Review recruitment materials (advertisements, posters)

Continuing Review

- Conduct annual (or more frequent if risk warrants) continuing review of ongoing trials
- Review Serious Adverse Event (SAE) reports and SUSARs (Suspected Unexpected Serious Adverse Reactions)
- Review protocol amendments and assess whether substantial amendments require re-review
- Assess any new safety information that may change the risk-benefit assessment
- Review interim analysis results (if applicable)
- Monitor enrollment rates and screen failure rates for unusual patterns

Other Functions

- Handle complaints and concerns raised by research participants

- Conduct site visits to trial sites to verify GCP compliance (in India: mandatory per NDCT Rules)
- Maintain records of all reviewed studies, minutes of meetings, decisions, and correspondence
- Coordinate with CDSCO and respond to regulatory authority queries
- Provide training to investigators and site staff on ethics in research

Types of Review by IRB/IEC

Review Type	When Used / Criteria
Full Board (Convened) Review	Default review type for all research involving more than minimal risk; requires quorum; all members review the application; decision by majority vote at formal meeting
Expedited Review	Research involving no more than minimal risk (e.g., minor protocol amendments, low-risk observational studies); conducted by Chairperson or a designated reviewer; no full board meeting required
Exemption from Review	Research exempt from full review: retrospective chart reviews, anonymized data analysis, educational testing; still requires determination of exemption by designated reviewer
Emergency Review	For urgent situations requiring immediate action to protect subject safety; may be done by phone/email; documented retrospectively at full board meeting

Working Procedures of IRB/IEC

STEP 1	<p>Application Submission</p> <p>Investigator submits complete application dossier to EC secretariat Documents: Completed EC application form, signed protocol, Investigator's Brochure, ICF (all versions, all languages), CVs of investigators, insurance certificate, regulatory approval (CDSCO IND/Form CT-04), sponsor letter, previous EC approvals (for multi-center), financial disclosure EC secretariat performs completeness check; assigns EC reference number and date</p>
STEP 2	<p>Pre-Meeting Review</p> <p>Member Secretary circulates application to all members at least 7-14 days before the meeting Members conduct independent review of assigned sections (scientific, ethical, statistical, participant welfare)</p>
STEP 3	<p>EC Meeting</p> <p>Scheduled at fixed intervals (at least once a month for active trial sites; NDCT 2019 requires monthly meetings) Investigator may be invited to present the study and answer questions Primary reviewer presents findings; discussion by all members Members with conflict of interest (financial, personal, professional) must declare and leave the room during discussion/vote Decisions: Approval Approval with modifications Disapproval Deferral (more information needed)</p>

STEP 4**Decision Communication**

EC issues written decision within 2 weeks of the meeting
Approval letter: includes conditions (if any), duration of approval (usually 1 year), requirements for continuing review
Disapproval/modification: detailed written justification; investigator has right to appeal or revise and resubmit
Approved ICF version number and date must be specified in approval letter

STEP 5**Continuing Review and Close-out**

Annual continuing review required for all active trials; investigator submits annual status report
EC reviews SAE reports, protocol amendments, and new safety information throughout trial
Final close-out review upon study completion; investigator submits final report with summary of findings
EC may suspend or terminate study if new evidence indicates unacceptable risk to participants

EC Registration in India (NDCT Rules 2019)

- All Ethics Committees conducting review of clinical trials must be registered with CDSCO under Rule 8 of NDCT Rules 2019
- Registration is granted for a period of 3 years; renewable
- CDSCO maintains a list of registered ECs; clinical trials can only be reviewed by registered ECs
- Unregistered EC approval is not valid for CDSCO clinical trial permission
- Registration suspended/cancelled if EC fails to comply with NDCT Rules requirements

Informed Consent Process and Procedures

Informed consent is the process by which a potential research participant voluntarily confirms their willingness to participate in a clinical trial after being fully informed about the nature, purpose, risks, benefits, alternatives, and their rights as a participant. Informed consent is both an ethical obligation and a regulatory requirement — it is not merely a signature on a form, but an ongoing interactive process.

Informed consent must be obtained BEFORE any trial-related procedures are performed, including screening tests. It is a process, not just a signature — the participant must be given adequate time and opportunity to ask questions and consider participation.

Ethical and Legal Basis

- Declaration of Helsinki (2013): Articles 25-32 — right to self-determination, voluntary participation, right to withdraw, special protections for vulnerable populations
- ICH E6(R2) GCP: Section 4.8 — detailed requirements for informed consent process and content
- Belmont Report (1979): Principle of Respect for Persons — individuals should be treated as autonomous agents; those with diminished autonomy are entitled to protection
- NDCT Rules 2019 (India): Rule 13 — informed consent mandatory; audio-visual recording of consent process required in certain situations
- Indian ICMR Guidelines (2017): Additional requirements including community consent, impartial witness, and specific provisions for vulnerable groups

Elements of Informed Consent (ICH E6 R2 — Section 4.8.10)

The Informed Consent Form (ICF) must contain the following 20+ required elements:

Element	Requirement
1. Experimental Nature	Statement that the trial involves research; explanation of the experimental nature of the investigational product
2. Objectives	Purpose of the trial; what the investigator is trying to find out
3. Treatment(s)	Description of the investigational product, dose, route of administration, all possible treatment group assignments including placebo
4. Procedures	All trial-specific procedures including those that are experimental
5. Reasonably Foreseeable Risks	All known and potential risks and discomforts to the subject and, where applicable, to an embryo, fetus, or nursing infant
6. Expected Benefits	Anticipated benefits of trial participation (or lack thereof) to the subject or others
7. Alternatives	Alternative procedures or treatments available to the subject outside the trial
8. Confidentiality	Extent of confidentiality of records; who will have access to records (sponsor, monitor, auditor, IRB/IEC, regulatory authority)
9. Compensation/Treatment for Injury	Availability of compensation and/or treatment if trial-related injury occurs; who provides them and how to obtain them

10. Contact Information	Contact details for further information: about the trial (investigator), about subject rights (IRB/IEC), about trial-related injury (sponsor/investigator)
11. Voluntary Participation	Participation is voluntary; refusal or withdrawal will not result in penalty or loss of benefits to which the subject is otherwise entitled
12. Ongoing Participation	Subject or their legally authorized representative will be informed in a timely manner if new information becomes available that may affect willingness to continue participation
13. Anticipated Duration	Expected duration of the subject's participation
14. Approximate Number of Subjects	Approximate number of subjects in the trial (site and overall)
15. AV Recording (India-specific)	In India (NDCT Rule 13): audio-visual recording of the consent process is required for new drugs and vaccines; subject must be informed of this recording

Informed Consent Process — Step by Step

1. Potential subject identified through screening of medical records, physician referral, or public advertisements
2. Investigator or designated staff member (trained in GCP) approaches potential subject
3. Private setting ensured — no coercion, undue influence, or time pressure
4. ICF provided: subject given copy of ICF to read; time allowed (may take copy home if needed)
5. Oral explanation provided in subject's language; all procedures, risks, benefits, alternatives explained clearly
6. Questions invited and answered honestly and completely
7. Subject's comprehension assessed — not just reading ability
8. If subject is willing to participate: subject (or LAR) signs and dates the ICF
9. Investigator/person obtaining consent signs and dates the ICF
10. Impartial witness signs if required (e.g., illiterate subject, vulnerable population)
11. Copy of signed ICF given to subject; original retained by site
12. In India: Audio-visual recording of consent process (NDCT Rule 13) for new drugs/vaccines — recording archived
13. If new information emerges during trial: Re-consent process initiated; subject given updated ICF

Special Considerations in Informed Consent

ILLITERATE SUBJECTS

Thumb Impression and Impartial Witness

Subject who cannot read but can understand information: thumb impression on ICF acceptable

An impartial witness must be present during the entire consent process

Impartial witness: person independent of the trial, not involved in the site staff, not unduly influenced by investigator

Witness signs and dates ICF confirming the process was explained adequately and consent was voluntary

In India: audio-visual recording additionally required per NDCT Rules 2019

**MINORS /
CHILDREN****Parental/Guardian Consent + Child Assent**

Legal guardian (parent/LAR) must provide informed consent on behalf of minor
Additionally, child assent (age-appropriate explanation and agreement) must be obtained from children who are capable of understanding (typically age 7 and above in India)

ICF for children: age-appropriate language; child-friendly format (pictures, simple words)

As the child matures: re-consent as adults when they reach legal age during the trial

**COGNITIVELY
IMPAIRED****LAR Consent + Subject Assent**

Legally Authorized Representative (LAR) provides consent when subject lacks capacity

Researchers must determine whether the subject has capacity to provide consent (not all cognitively impaired individuals lack capacity)

Subject assent (if capable) must be obtained in addition to LAR consent

Consent must be re-evaluated if subject regains capacity

**EMERGENCY
RESEARCH****Exception from Informed Consent**

When subject is in life-threatening situation and cannot give consent (unconscious, critical emergency)

LAR must provide consent; if LAR unavailable: waiver of consent may be granted by IRB/IEC

Emergency waiver requires: life-threatening situation, no available standard treatment, research not practicable without waiver

Subject must be informed and consent obtained as soon as practically possible

**VULNERABLE
POPULATIONS****Additional Protections Required**

Prisoners, students, employees of sponsor/investigator, terminally ill, economically disadvantaged

Additional safeguards: heightened scrutiny by IRB/IEC, independent patient advocate, minimum risk requirement

No undue inducement: compensation must be reasonable; not so large as to constitute undue influence

ICMR Guidelines 2017 (India): specific protections for tribal communities, economically backward populations, and persons in dependent relationships

Right to Withdraw

- Participants have the unconditional right to withdraw from a trial at any time without penalty or loss of benefits
- Withdrawal must be documented in the source documents and CRF
- Investigators should inquire about the reason for withdrawal (for safety and data integrity) but cannot compel disclosure
- Data already collected may be used unless the participant explicitly objects
- Regulatory requirement: withdrawal does not affect the participant's standard medical care

GCP Obligations of Investigators, Sponsors, and Monitors

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials involving human subjects. Compliance with GCP ensures that the rights, safety, and well-being of trial subjects are protected, and that the clinical trial data are credible. ICH E6(R2) is the globally accepted GCP guideline.

ICH E6(R2) GCP (adopted 2016) emphasizes risk-based quality management, the sponsor's and investigator's responsibilities for trial oversight, and the primacy of subject protection throughout all trial activities.

GCP Obligations of the Investigator

The investigator is the person responsible for the conduct of the clinical trial at the trial site. A Principal Investigator (PI) is responsible when a trial is conducted by a team. Sub-Investigators work under the PI's supervision.

Qualifications and Agreements

- Must be adequately qualified (education, training, experience) to conduct the trial
- Must have sufficient time and resources to conduct the trial properly
- Must have access to adequate number of eligible subjects during the enrollment period
- Must have adequate staff and facilities for trial conduct
- Must sign the Protocol Signature Page and Investigator's Agreement with the sponsor
- Must sign Form FDA 1572 (US) / Form CT-04 declaration (India) committing to GCP compliance

Compliance Obligations

- Protocol compliance: Must conduct the trial in accordance with the protocol; document any deviations
- Informed consent: Must ensure proper informed consent obtained before trial procedures; re-consent for new information
- Investigational Product (IP) management: Accountable for all IP dispensed at site; maintain IP accountability records; ensure proper storage conditions
- Medical care: Ensure all trial-related medical decisions are made by qualified physicians; responsible for ongoing medical care of subjects
- Subject protection: Promptly report SAEs to sponsor (within 24 hours); may unblind in medical emergency

Documentation and Reporting

- Source documents: Maintain complete, accurate, legible, dated source documents; allow monitor/auditor/inspector access
- Case Report Form (CRF): Complete CRF entries promptly, accurately; explain any changes (date, reason, initials)
- SAE reporting: Report all SAEs to sponsor within 24 hours of awareness; complete SAE form; assess causality
- Progress reports: Submit progress reports to IRB/IEC annually (or per local requirements)
- Deviations: Report all protocol deviations to sponsor and IRB/IEC promptly
- Premature termination: If investigator terminates trial early, must notify sponsor, IRB/IEC, and regulatory authority with reasons

Investigator's Brochure (IB)

- Investigator must have current version of the IB available at the trial site at all times
- Must read and understand all IB updates issued by sponsor during the trial
- IB informs investigator's clinical judgment during the trial

GCP Obligations of the Sponsor

The sponsor is an individual, company, institution, or organization that takes responsibility for the initiation, management, and financing of a clinical trial. The sponsor may delegate trial activities to a Contract Research Organization (CRO) but cannot delegate ultimate responsibility.

Quality Management System (QMS)

- Implement a quality management system (QMS) throughout all trial-related activities
- Perform risk assessment: identify critical protocol elements and risks to subject safety and data integrity
- Implement risk-based monitoring plan: focus monitoring resources where risks are highest
- Establish SOPs (Standard Operating Procedures) for all trial activities

Investigational Product Management

- Characterize the IP: manufacture, test, and label the IP in compliance with GMP and regulatory requirements
- IP accountability: Maintain records of all IP manufactured, shipped, received, dispensed, returned, and destroyed
- Blinding/unblinding: Maintain blind; document unblinding code procedures for emergencies
- Handling complaints: Investigate and act on all quality-related complaints about IP

Regulatory Submissions

- Prepare and submit IND/CTA/Form CT-04 application to regulatory authority before initiation
- Obtain EC/IRB approval before trial initiation at each site
- Report SUSARs (Suspected Unexpected Serious Adverse Reactions) to regulatory authorities and all investigators within 7 days (fatal/life-threatening) or 15 days (other)
- Submit Annual Safety Reports (ASRs) / Development Safety Update Reports (DSURs) per ICH E2F
- Submit NDA/ANDA/MAA using trial data upon completion of development program

Monitoring and Oversight

- Appoint monitor(s) to oversee trial conduct at each site
- Review monitoring reports; take action on findings; follow up on outstanding issues
- Establish audit function: periodic audits of trial sites, sponsor systems, and CRO operations
- Trial Master File (TMF): Establish and maintain TMF containing all essential documents per ICH E6 Appendix
- Data management: Establish validated data management system; implement data validation checks

Premature Termination by Sponsor

- Must notify investigators, regulatory authority, and IRB/IEC of early termination with reasons
- Must ensure subjects receive proper follow-up care and are informed about termination
- Must follow up on SAEs occurring after termination that are trial-related

GCP Obligations of the Monitor (Clinical Research Associate — CRA)

The monitor (or Clinical Research Associate, CRA) is a person appointed by the sponsor to oversee the progress of the clinical trial. Monitoring is the act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable regulatory requirements.

Qualifications of Monitor

- Clinical background: scientific or medical training; knowledge of pharmacology, GCP, regulatory requirements
- Sponsor-specific training on the protocol, therapeutic area, IP, and sponsor's SOPs
- Typically: Bachelor's or Master's in pharmacy, life sciences, nursing, or medicine; 2+ years clinical research experience

Monitoring Activities

Monitoring Activity	Details
Site Initiation Visit (SIV)	Before enrollment begins; verify site readiness; train staff on protocol; confirm EC/IRB and regulatory approvals; verify IP storage; review ICF versions
Routine Monitoring Visits (RMV)	Ongoing during trial; SDV (Source Data Verification); IP accountability check; review CRFs for accuracy and completeness; discuss protocol compliance; review AE/SAE documentation
Source Data Verification (SDV)	Comparing CRF entries against source documents to verify accuracy, completeness, and consistency; identifies data entry errors and protocol deviations
IP Accountability Check	Verify IP received, stored, dispensed, and returned per protocol; count remaining IP; check temperature logs; ensure chain of custody
Site Close-out Visit	At end of trial or site termination; ensure all data queries resolved; verify IP reconciliation complete; archive instructions given; ensure all required documents in ISF
Remote Monitoring	Electronic review of data entered in EDC (Electronic Data Capture) system; triggered queries; review of centralized monitoring alerts; used as complement to on-site monitoring

Monitoring Reports

- Written monitoring report to sponsor within a defined timeframe after each visit (typically 5-10 business days)
- Contents: Date and type of visit, investigator/site staff met, findings, deviations, IP status, recommendations, follow-up actions required

- Follow-up letter: Written to investigator following each monitoring visit, documenting outstanding issues and required actions with deadlines
- Escalation: Unresolved critical issues escalated to sponsor's medical/regulatory team or management

Managing and Monitoring Clinical Trials

Clinical trial management encompasses all administrative, logistical, and operational activities required to successfully plan, initiate, execute, and close a clinical trial in compliance with the protocol, GCP, and regulatory requirements. Effective management ensures subject safety, data quality, regulatory compliance, and timely completion.

Clinical Trial Management System (CTMS)

- **Definition:** A software system used to manage clinical trial data including patient enrollment, site management, monitoring activities, regulatory submissions, and financial tracking
- **Functions:** Study planning and timeline tracking, subject randomization, IP dispensing records, site contact management, document management, regulatory submission tracking, financial management (budget, invoicing)
- **Examples:** Medidata Rave, Oracle Siebel CTMS, Veeva Vault CTMS, Medrio

Electronic Data Capture (EDC)

- **Definition:** A computerized system for collecting clinical trial data electronically (replacing paper CRFs)
- **Advantages:** Real-time data entry, automatic data validation, remote monitoring capability, faster database lock, audit trail, reduced transcription errors
- **Examples:** Medidata Rave, Oracle InForm, REDCap, OpenClinica, Veeva EDC
- **Requirements:** 21 CFR Part 11 compliance (FDA): electronic records/signatures must be trustworthy, reliable, equivalent to paper

Essential Documents for Clinical Trial Management

ICH E6(R2) Appendix lists 26 essential documents that must be on file for each clinical trial. These documents are maintained in:

- Trial Master File (TMF): Maintained by sponsor; contains all essential documents for the entire trial
- Investigator Site File (ISF): Maintained by investigator at the site; contains site-level essential documents

Document Category	Documents	Location
Before Trial Start	Signed Protocol + Amendments, Investigator's Brochure, ICF (all versions), EC/IRB approval, Regulatory authority approval (IND/Form CT-04), Investigator's CV, Normal value reference ranges, IP certificate of analysis, IP labeling, IP shipping records	TMF + ISF
During Trial	Signed informed consent forms, CRFs/eCRFs, Source documents, SAE reports, Protocol deviation	TMF + ISF

	reports, Monitoring visit reports, IP accountability logs, Temperature logs (IP storage), Correspondence (sponsor-site, EC-site)	
After Trial Completion	Final protocol deviation list, SAE reconciliation list, Statistical analysis plan (final), Clinical study report, IP final reconciliation, EC close-out notification, Archiving records	TMF (final)

Risk-Based Monitoring (RBM)

Risk-Based Monitoring (RBM) is a modern, efficient approach to clinical trial monitoring that focuses monitoring resources on the highest-risk aspects of a trial, rather than conducting 100% source data verification (SDV) at every visit. Endorsed by ICH E6(R2), US FDA (2013 guidance), and EMA (2013 guideline).

- Risk identification: Identify critical data and critical processes in the protocol (e.g., primary endpoint data, safety data, randomization, consent)
- Centralized monitoring: Statistical review of accumulating data across all sites; identify data anomalies, outliers, missing data patterns, and unusual trends
- On-site monitoring: Targeted to high-risk sites or specific data issues identified by centralized monitoring; 100% SDV only for critical data elements
- Remote monitoring: Review of EDC data remotely; electronic document review via eTMF; triggered by centralized monitoring signals
- Monitoring plan: Must be documented in a formal Clinical Trial Monitoring Plan specifying frequency, method, and focus areas for each site

Protocol Deviation Management

Deviation Type	Definition	Action Required
Major/Important Protocol Deviation	Deviations that significantly affect subject safety or integrity of trial data (e.g., enrollment of ineligible subject, missed primary endpoint assessment, GCP non-compliance)	Immediate report to sponsor and EC/IRB; CAPA implementation; regulatory authority notification if required; may require exclusion from per-protocol analysis
Minor Protocol Deviation	Deviations that do not significantly affect subject safety or data integrity (e.g., late PK sample, minor visit window violation)	Document in source and CRF; note in monitoring report; cumulative review for patterns
Protocol Violation	Serious non-compliance with protocol or GCP; may result in site termination, audit, or regulatory action	Immediate investigation; CAPA; may require subject withdrawal; possible regulatory reporting

Data Safety Monitoring Board / Committee (DSMB/DSMC)

A Data Safety Monitoring Board (DSMB) is an independent group of experts that reviews accumulating efficacy and safety data from an ongoing clinical trial to ensure continued safety of participants and scientific validity of the trial.

- **Composition:** Independent experts: biostatistician, clinical expert(s) in therapeutic area, ethicist; NOT affiliated with sponsor or investigator team
- **Functions:** Review unblinded interim data; assess emerging safety signals; recommend early stopping for overwhelming efficacy, futility, or safety concerns
- **Stopping Rules:** Pre-specified statistical criteria (O'Brien-Fleming, Haybittle-Peto boundaries) for early stopping at interim analyses
- **Required for:** Phase III trials with definitive efficacy endpoints; trials in vulnerable populations; long-term trials; trials with high-risk IP; all trials evaluating mortality endpoints
- **Reports:** DSMB produces open report (non-confidential safety summary for sponsor) and closed report (unblinded analysis for DSMB only)

Pharmacovigilance — Safety Monitoring in Clinical Trials

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. In the context of clinical trials, pharmacovigilance encompasses all safety monitoring activities during the conduct of the trial to protect the safety of research participants and inform the benefit-risk assessment of the investigational product.

The WHO defines pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'. In clinical trials, safety monitoring is a regulatory requirement under ICH E6(R2), ICH E2A, and national regulations.

Definitions

Term	Definition (ICH E2A / ICH E6)
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial subject administered an investigational product; does NOT necessarily have a causal relationship with the treatment
Adverse Drug Reaction (ADR)	In the pre-approval context: all noxious and unintended responses to a medicinal product related to any dose; causal relationship cannot be ruled out
Serious Adverse Event (SAE)	Any untoward medical occurrence that: results in death is life-threatening requires hospitalization or prolongation of existing hospitalization results in persistent or significant disability/incapacity is a congenital anomaly/birth defect is an important medical event (Jeopardizes patient; requires medical or surgical intervention to prevent one of the above outcomes)
Suspected Unexpected Serious Adverse Reaction (SUSAR)	SAE with a reasonable possibility of causal relationship with the IP AND unexpected (not listed in IB or labeling) AND serious
Expected SAR	SAR whose nature and severity is consistent with information in the IB/product labeling
Unexpected SAR	SAR whose nature or severity is NOT consistent with the IB; includes class-effect reactions not listed for that specific IP

Life-threatening AE	AE that puts subject at immediate risk of death at time of occurrence
Causality Assessment	Investigator's assessment of whether a causal relationship between the IP and the AE is possible; categories: Definite, Probable, Possible, Unlikely, Not Related

Adverse Event Classification

Severity Grading (NCI CTCAE v5.0)

Grade	Severity	Description
Grade 1	Mild	Asymptomatic or mild symptoms; no intervention indicated; does not limit activities
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death	Death related to AE

Seriousness (5 Criteria — ICH E2A)

- Death
- Life-threatening (at time of occurrence)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Important medical event (may require adding this per medical judgment even if not fitting above criteria)

Distinction: Severity and Seriousness are DIFFERENT. Severity = intensity of the AE (Grade 1-5). Seriousness = whether the AE meets regulatory criteria (SAE = serious). An AE can be severe (Grade 4) but not an SAE, or an SAE can be of mild severity (e.g., hospitalization for observation).

SAE Reporting Requirements

From / To	Timeline	Regulatory Basis
Investigator to Sponsor	Immediate (within 24 hours) for all SAEs; initial SAE report with available information; follow-up reports as new information available	ICH E6(R2) Section 4.11; NDCT Rules 2019 Rule 21
Sponsor to Regulatory Authority (SUSAR — Fatal/Life-threatening)	Within 7 calendar days of first receipt of information (IND Safety Report); follow-up within 8 additional days (total 15 days)	ICH E2A; 21 CFR 312.32 (US); NDCT Rule 21 (India)

Sponsor to Regulatory Authority (SUSAR — Other serious/unexpected)	Within 15 calendar days of first receipt of information	ICH E2A; 21 CFR 312.32; NDCT Rule 21
Sponsor to All Investigators	SUSAR information must be shared with all investigators participating in the trial; allows re-assessment of risk-benefit at each site	ICH E6(R2) Section 5.17; NDCT Rules 2019
Investigator to IRB/IEC	SAE/SUSAR reports forwarded to IRB/IEC per local requirements; typically within 7-15 days; IRB/IEC may require expedited reporting of certain events	ICH E6 Section 4.11.2; NDCT Rules 2019
Sponsor — Annual Safety Report (DSUR)	Development Safety Update Report (DSUR) per ICH E2F submitted annually on the International Birth Date (IBD) of the IND	ICH E2F; FDA/EMA/PMDA requirements

Development Safety Update Report (DSUR)

- **Definition:** A periodic safety report submitted by the sponsor annually during clinical development to provide a comprehensive, integrated summary of safety data accumulated during the reporting period
- **ICH Guideline:** ICH E2F (2011) — Development Safety Update Report; adopted by FDA, EMA, PMDA
- **Periodicity:** Annual; based on International Birth Date (IBD) — date of first authorization of any trial of the IP worldwide
- **Contents:** Summary of clinical development program, cumulative subject exposure, all serious adverse events, SUSARs, safety-related protocol amendments, important safety issues, benefit-risk assessment, plans for risk management
- **Replaces:** Individual IND Annual Reports (US); Clinical Trial Certificates Annual Reports; Drug Safety Update Reports

Safety Monitoring Tools and Methods

Method	Description / Application
MedDRA Coding	Medical Dictionary for Regulatory Activities; standardized medical terminology for coding AEs, medical history, indications; used in all regulatory submissions; facilitates signal detection across trials
CIOMS Forms	Council for International Organizations of Medical Sciences (CIOMS) I Form: standardized international SAE/SUSAR reporting form; used for expedited safety reporting to regulatory authorities
Signal Detection	Systematic process to identify new or changed safety signals from accumulated safety data; disproportionality analysis (ROR, PRR), Bayesian methods (BCPNN, GPS), clinical review
Data Safety Monitoring Board (DSMB)	Independent expert group reviewing unblinded accumulating data; protects subjects from unforeseen harm; maintains scientific validity; can recommend early stopping
Pharmacovigilance Plan	Risk management strategy developed by sponsor; identifies known risks, potential risks, missing information; specifies routine and additional PV activities; required as part of Risk Management Plan (RMP) in EU

Benefit-Risk Assessment	Ongoing evaluation of benefit-risk balance of IP in light of accumulating safety and efficacy data; consideration for DSMB, sponsor, and regulators
Sentinel Events	Pre-specified safety events that, if observed, trigger automatic sponsor review; may result in immediate protocol modification, dose reduction, or trial suspension

Pharmacovigilance in India — PvPI

India operates the Pharmacovigilance Programme of India (PvPI) for post-marketing surveillance. For clinical trials, safety monitoring is governed by NDCT Rules 2019.

- PvPI: Established in 2010; National Coordination Centre (NCC) at IPC (Indian Pharmacopoeia Commission), Ghaziabad
- ADR reporting portal: VigiFlow (WHO-UMC platform); accessible to HCPs and patients
- CDSCO Vigilance: During clinical trials, SAE/SUSAR reports submitted to CDSCO and the relevant EC
- Trial-related compensation: NDCT Rules 2019 mandate compensation for trial-related injury or death; formula for compensation specified in Appendix XI of Schedule Y (legacy)
- Audit by CDSCO: CDSCO may inspect clinical trial sites and sponsor offices for PV compliance

ICH Safety Guidelines for Clinical Trials

ICH Guideline	Topic
ICH E1	The Extent of Population Exposure to Assess Clinical Safety — minimum exposure database for drug approval
ICH E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting — SAE/SUSAR definitions and timelines
ICH E2B(R3)	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs) — electronic safety reporting format (HL7 format; EudraVigilance)
ICH E2C(R2)	Periodic Benefit-Risk Evaluation Report (PBRER) — post-marketing periodic safety report
ICH E2D	Post-Approval Safety Data Management — expedited reporting post-approval
ICH E2E	Pharmacovigilance Planning — PV plan development and RMP
ICH E2F	Development Safety Update Report (DSUR) — annual safety reporting during clinical development
ICH E6(R2)	Good Clinical Practice — Section 4.11 (investigator safety reporting), Section 5.17 (sponsor safety reporting)

— Best Of Luck For Your Exam —

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