PharmacoLearn

MPL204T Clinical Research and Pharmacovigilance, M.Pharm Semester 2

Unit 1: Regulatory Perspectives of Clinical Trials

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Clinical Research and Pharmacovigilance, subject code MPL204T, is a core Semester 2 subject of M.Pharm Pharmacology. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject joins the two disciplines that guard a medicine at the two ends of its life in humans. Clinical research generates the evidence: a candidate drug is tested in people, under rules strict enough that the results can be believed and the participants protected while they are generated. Pharmacovigilance keeps the guard up afterwards: once a medicine is marketed to millions, rare and delayed harms that no trial could have caught must be detected, assessed and acted on for as long as the drug is used. Unit 1 sets out the regulatory and ethical frame of trials: the origin and principles of ICH Good Clinical Practice, ethics committees, the Schedule Y and ICMR framework in India, and the informed consent process. Unit 2 studies trial types and designs, experimental and observational, and the study team that runs them. Unit 3 works through trial documentation, monitoring and safety monitoring, and then the adverse drug reaction itself: its types, detection, reporting, assessment and management. Unit 4 turns to pharmacovigilance proper: its history, its terminologies, the WHO programme, medication safety evaluation, and how pharmacovigilance centres are established in hospitals, industry and national programmes. Unit 5 covers the working methods and tools: surveillance of every kind, spontaneous reporting, the safety databases Argus and Aris G, the reporting system VigiFlow, and the statistical evaluation of safety data. Unit 6 closes with the three population disciplines the syllabus names: pharmacoepidemiology, pharmacoeconomics and safety pharmacology.

1.1 Why trials are regulated: the ethical history in brief

A clinical trial is an experiment performed on people, and its rules were written in response to experiments that shamed medicine. Three landmarks frame everything in this unit. The **Nuremberg Code (1947)**, drawn from the trial of Nazi physicians, stated the first modern rule: the voluntary consent of the human subject is absolutely essential. The **Declaration of Helsinki (1964)**, issued by the World Medical Association and revised repeatedly since, became the physician's ethical charter for research: independent committee review, informed consent, and the principle that the subject's welfare outranks the interests of science and society. The **thalidomide disaster (1961)**, in which a sedative marketed as safe caused severe limb malformations in thousands of children, was a drug safety failure rather than a consent failure, and it drove the modern licensing state: in the United States the Kefauver Harris Amendments of 1962 required proof of efficacy as well as safety before marketing.

The regulatory system of this subject is the accumulated answer to those lessons. Ethics rules protect the person in the trial; good clinical practice rules protect the truth of the data; licensing and pharmacovigilance rules protect the patients who come after. A student who keeps those three protections separate in mind will find the rest of the subject organizes itself.

1.2 The origin of ICH and the idea of harmonization

By the 1980s a new drug faced three separate development programmes for the United States, Europe and Japan, with duplicated trials, different data formats and different technical demands, while the science underneath was the same. The **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use**, universally shortened to **ICH**, was

founded in 1990 to end that duplication: regulators and industry associations of the three regions agreed to write one set of technical guidelines together, so that data generated once could support registration everywhere. ICH (renamed the International Council for Harmonisation when it reformed as a legal association in 2015) works through expert working groups whose guidelines are adopted region by region. Its guideline families are quality (Q), safety (S), efficacy (E) and multidisciplinary (M). Clinical research lives mainly in the E family, and its most consequential member is **E6, the Guideline for Good Clinical Practice**, adopted in 1996 and cited in the PCI reference list for this subject.

Harmonization matters to a pharmacology student for a practical reason: an Indian trial conducted to ICH-GCP can support a global dossier, and an Indian pharmacovigilance report written in ICH formats can enter the world safety system. The local rules of sections 1.6 and 1.7 are India's implementation of the same ideas, not a rival system.

1.3 ICH-GCP: what good clinical practice is

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human subjects. ICH E6 states its purpose in one sentence: compliance gives public assurance that the rights, safety and well being of trial subjects are protected, consistent with the Declaration of Helsinki, and that the clinical trial data are credible. Protection of people and credibility of data are the twin aims, and every GCP rule serves one or the other.

The guideline's heart is its **thirteen principles**. Grouped for learning, they are:

Group	The principles it gathers
Ethics first	Trials are conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with GCP and regulatory requirements; before a trial begins, foreseeable risks are weighed against anticipated benefit, and the trial proceeds only if benefit justifies risk; the rights, safety and well being of subjects prevail over the interests of science and society
Independent review and consent	A trial is reviewed and given favourable opinion by an institutional review board or independent ethics committee before it starts; freely given informed consent is obtained from every subject before participation
Sound science and qualified people	Trials are scientifically sound and described in a clear, detailed protocol; medical care and decisions are the responsibility of a qualified physician; every individual involved is qualified by education, training and experience; the trial is conducted in compliance with the approved protocol
Product and data integrity	The investigational product is manufactured, handled and stored to applicable good manufacturing practice and used as the protocol directs; information is recorded, handled and stored so that accurate reporting, interpretation and verification are possible; records identifying subjects are kept confidential; systems with procedures assuring quality are implemented in every aspect of the trial

Examiners ask for the principles themselves, so the grouping above is a memory aid, not a substitute: the thirteen are conventionally listed individually, and a good answer names them in order before explaining them in groups.

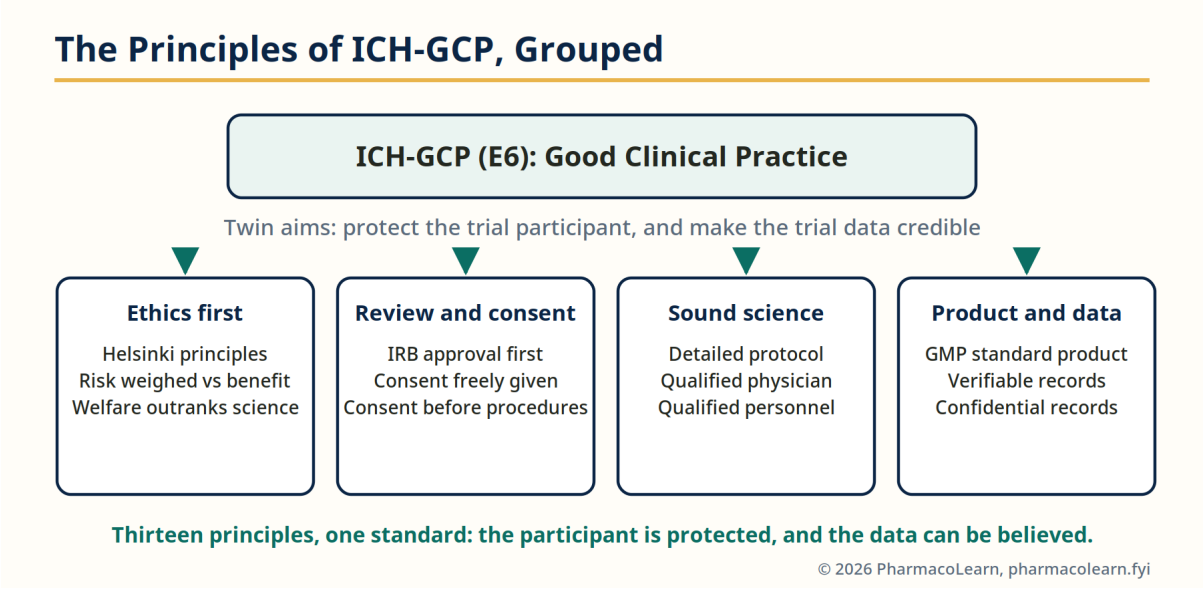

Figure: The principles of ICH-GCP (E6) grouped by what they protect: the participant, the review process, the science, and the product and its data.

1.4 GCP in India

India's own **GCP guidelines**, issued by the Central Drugs Standard Control Organization (CDSCO) in 2001 and named in this subject's reference list, adapt the same standard to Indian law and institutions: they restate the ICH principles, define the responsibilities of sponsor, investigator and ethics committee in the Indian setting, and require ethics committee review and informed consent for trials conducted in India. In daily practice an Indian trial runs under three layers at once: the international standard (ICH-GCP), the Indian GCP guidelines, and the statute law of section 1.6. Where they differ in detail, the law governs; where the law is silent, GCP is the working rule.

1.5 The ethics committee: institutional review board

No trial in this framework begins on a researcher's word alone. An **ethics committee**, called an **Institutional Review Board (IRB)** in the American terminology the syllabus uses and an Institutional Ethics Committee in Indian usage, is the independent body charged with protecting the rights, safety and well being of participants. It reviews the protocol, the investigator's qualifications and brochure, the consent documents and the plans for recruitment and compensation, and it must approve the trial before the first participant is enrolled; its oversight continues through the trial by review of amendments, progress reports and serious adverse events, and it can suspend or terminate approval.

A properly constituted committee is deliberately mixed: medical and non medical members, scientific and lay members, including a member from outside the institution and a person able to represent the participant's perspective, with a chairperson from outside the institution under the Indian rules, so that no single professional interest dominates. Its judgements are ethical, not merely technical: whether the risk benefit balance is acceptable, whether the consent form is honest and comprehensible in the local language, whether vulnerable participants are adequately protected, and whether the trial answers a question worth asking people to bear risk for. The committee's records, composition and procedures are themselves regulated, because an unaccountable committee would reproduce the problem it exists to solve.

1.6 Schedule Y and the Indian regulatory framework

Clinical trials in India are conducted under the Drugs and Cosmetics Act framework. **Schedule Y** of the Drugs and Cosmetics Rules was, for decades, the schedule that prescribed the requirements and guidelines for permission to import or manufacture new drugs for sale and to conduct clinical trials: the data to be submitted, the phases of study, the responsibilities of sponsor and investigator, and the format of reports. The clinical trial provisions of Schedule Y have since been replaced by a dedicated modern code, the **New Drugs and Clinical Trials Rules, 2019**, which now govern permission from the Central Licensing Authority (the Drugs Controller General of India, heading CDSCO), ethics committee registration, compensation for trial related injury, and timelines for decisions. The syllabus names Schedule Y because the subject's text predates the change; the student should know Schedule Y as the historical and still referenced framework and the 2019 Rules as the operative one. In both, the structure is the same: prior permission, registered ethics committee approval, informed consent, and safety reporting are legal duties, not courtesies.

1.7 The ICMR ethical guidelines

The **Indian Council of Medical Research (ICMR)** issues the ethical layer of the framework: the Ethical Guidelines for Biomedical Research on Human Subjects (2000, the edition in this subject's reference list; revised as the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017). Where Schedule Y and its successor rules say what permission is needed, the ICMR guidelines say what is ethical: the principles of autonomy, beneficence, non maleficence and justice applied to Indian research realities, consent in languages participants actually speak, special protection for children, pregnant women, tribal and other vulnerable populations, and rules for research in emergencies, on stored samples and on genetic material. Ethics committees in India judge protocols against the ICMR guidelines; regulators judge applications against the rules; a compliant trial satisfies both.

1.8 The informed consent process: structure and content

Informed consent is a process, not a signature: a dialogue in which a prospective participant is told what the trial involves, has the chance to ask questions, and freely agrees or declines. The document that records it, the informed consent form with its participant information sheet, has a standard content fixed by GCP and the Indian rules. Its essential elements are:

- The trial's purpose, and that it is research, distinct from ordinary treatment
- What will be done: procedures, visits, tests, and how long participation lasts
- Randomization and placebo, explained plainly where they apply
- Foreseeable risks and discomforts, and anticipated benefits, including the possibility of no personal benefit
- The alternative treatments available outside the trial
- Compensation and medical management for trial related injury, and any payments or costs to the participant
- Confidentiality: who will see the records, and its limits
- That participation is voluntary, that refusal costs nothing in ordinary care, and that the participant may withdraw at any time without giving a reason
- Whom to contact about the trial, about rights, and in case of injury

Consent is taken in a language the participant understands, by a person able to answer questions, with time to decide; for participants who cannot read, an impartial witness is present through the process and signs to that effect, and for those who cannot consent, a legally acceptable representative consents in their place under stricter safeguards. In India, audio visual recording of the consent process is additionally

required for specified categories of trials under the 2019 Rules. A consent taken badly is not a technical defect: it means the participant was never truly enrolled, ethically, at all.

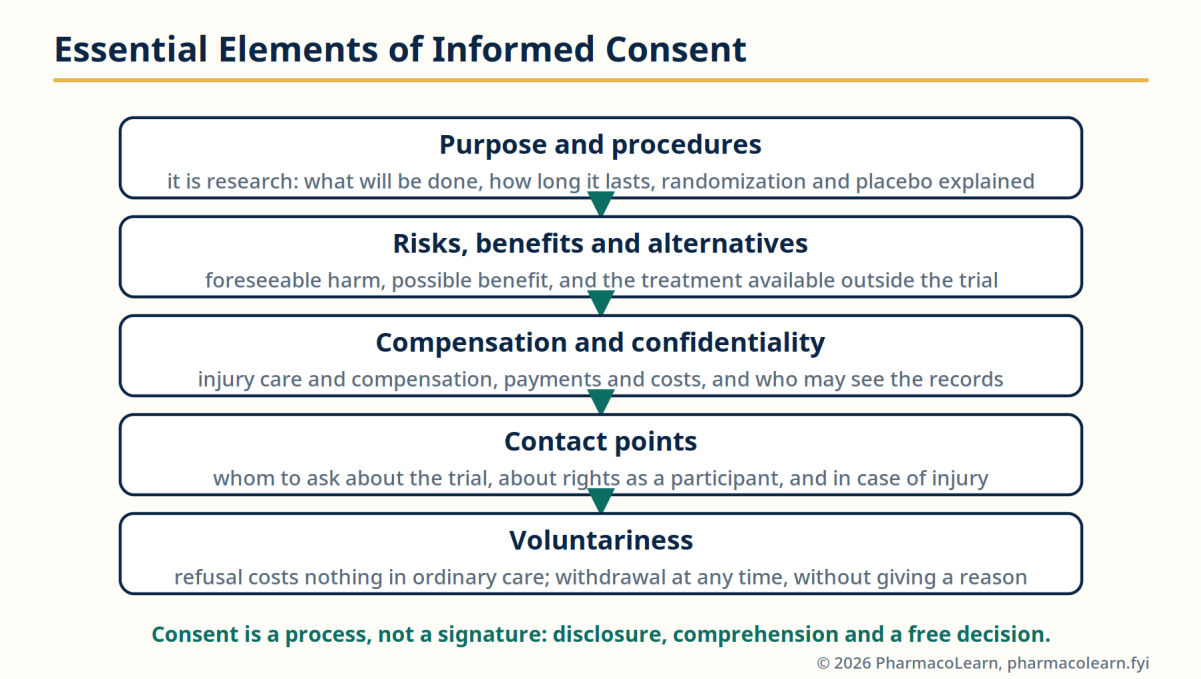

Figure: The essential elements of the informed consent process, from disclosure of purpose and procedures to the standing right to withdraw.

1.9 The ethical principles governing consent

Four principles govern the process and explain why its elements are what they are. **Autonomy** (respect for persons) is the root: a competent adult decides what is done to his or her own body, and consent is that decision made real. **Disclosure** follows: the decision is only the participant's if it rests on the material facts, which is why the element list of section 1.8 is mandatory rather than generous. **Comprehension** disciplines the telling: information dumped in medical language on a frightened patient is disclosed but not understood, so consent requires language, time and questions. **Voluntariness** excludes coercion and undue inducement: no threat to ordinary care, and no payment so large it blinds judgement. Together they convert the Nuremberg sentence, consent is absolutely essential, into a working method, and the same four principles reappear wherever this subject faces an ethical choice, from placebo use to research in vulnerable populations.

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THE PATH OF A TRIAL BEFORE THE FIRST PARTICIPANT

  Sponsor drafts protocol and investigator brochure
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      v
  Ethics committee (IRB) review: science, risk and benefit,
  consent documents, investigator suitability
      |
      v
  Regulatory permission (in India, the Central Licensing
  Authority under the NDCT Rules 2019)
      |
      v
  Site initiation: trained team, product, forms, systems
      |
      v
  Informed consent of each participant, freely given,
  before any trial procedure
      |
      v
  The trial may begin
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