

Unit 2: Ethics in Clinical Research

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2.1 Why the ethics is written down

No other science writes its conscience into law the way clinical research does, and the reason is the syllabus's opening list: the rules were each written over a documented failure. The pattern of this unit is therefore historical first and structural second. A code follows an atrocity or a disaster; the code hardens into committee review, consent doctrine and guideline; and the modern machinery of sections 2.11 to 2.15, the ethics committee, the safety board, the consent form, is the institutional form of memories the profession has sworn not to repeat. A regulatory affairs student should learn the history as law, not as colour: an assessor who knows why a rule exists applies it correctly to the case the rulebook did not foresee.

2.2 Historical perspectives I: the Nuremberg Code and the Nazi trials

The syllabus lists the Nazi trials and the Nuremberg Code side by side because the second is the direct product of the first. At the Nuremberg Doctors' Trial (1946 to 1947), physicians were tried for experiments conducted on concentration camp prisoners without consent: freezing, infection, mutilation and killing presented as research. The judgment of 1947 answered with the **Nuremberg Code**, ten points that remain the seed of all research ethics. Its first and governing point is that the **voluntary consent of the human subject is absolutely essential**: competent, informed, uncoerced. The remaining points require that the experiment yield fruitful results unprocurable by other means, rest on prior animal work, avoid unnecessary suffering, never proceed where death or disabling injury is expected, keep risk proportional to the humanitarian importance of the question, be conducted only by qualified persons, and stop at once if continuation threatens the subject, who must be free to withdraw at any time. Two limits of the Code explain the rest of this unit: it was a judgment, not a regulation, with no machinery to enforce it; and its absolute consent rule left unanswered the hard cases, research on those who cannot consent, that later instruments had to face.

2.3 Historical perspectives II: the thalidomide disaster

Thalidomide, marketed from 1957 as a sedative and taken for morning sickness, was withdrawn in 1961 after the recognition that it caused phocomelia, catastrophic limb malformation, in the children of women who took it in early pregnancy: some ten thousand affected children worldwide is the standard estimate. The regulatory lessons were permanent and are examinable as such. Safety testing before marketing had been inadequate to the exposure that followed, and in the United States the disaster was largely averted because a single FDA reviewer, Frances Kelsey, withheld approval for want of sufficient safety evidence. The legislative consequence in the United States was the Kefauver Harris Amendments of 1962, which added the requirement of **substantial evidence of effectiveness** from adequate and well controlled investigations to the pre existing requirement of safety, and tightened consent requirements for investigational drugs. Thalidomide also fixed two permanent features of the modern system: suspicion of any drug exposure in pregnancy, with the contraception and pregnancy testing regimes that follow from it, and the understanding that rare and delayed harms surface only in large exposed populations.

2.4 Historical perspectives III: the Tuskegee syphilis study

The **Tuskegee syphilis study** (1932 to 1972), run by the United States Public Health Service in Alabama, followed hundreds of poor African American men with syphilis, and a comparison group without it, for forty years, without informed consent, deceiving them about their diagnosis and about the "treatment" they were said to receive, and, the unforgivable core of it, continuing to withhold effective therapy after penicillin became the standard cure in the 1940s, actively keeping the men from obtaining it elsewhere. Exposed by the press in 1972, the study's consequences were structural: the National Research Act of 1974 created the commission whose work produced the Belmont Report (next section), and federal regulation of human research, institutional review boards and formal consent requirements, followed in the United States. Tuskegee is the standing proof of two propositions the whole subject rests on: that the investigators' scientific aim never licences deception or withheld treatment, and that the vulnerability of the population studied is itself an ethical fact, the seed of the special populations doctrine of section 2.10.

2.5 The Belmont Report: three principles

The **Belmont Report** (1979), issued by the United States National Commission for the Protection of Human Subjects, converted the history into principle. It drew the boundary between practice and research, and stated three principles that still organise every ethics discussion in this subject. **Respect for persons:** individuals are autonomous agents whose choices are to be honoured, operationalised as informed consent; and persons with diminished autonomy are entitled to protection, the principle behind the safeguards of section 2.10. **Beneficence:** the obligation to secure well being, to maximise possible benefits and minimise possible harms, operationalised as systematic risk benefit assessment. **Justice:** fairness in the distribution of the burdens and benefits of research, so that the populations who bear the risk are not chosen for their availability while others take the benefit, the principle Tuskegee violated in its purest form.

2.6 The Declaration of Helsinki

The **Declaration of Helsinki**, adopted by the World Medical Association in 1964 and revised repeatedly since (most recently in 2024), is the physician directed companion to Nuremberg: the ethical principles for medical research involving human participants, addressed to doctors and incorporated by reference into regulations and guidelines worldwide, including the consent and committee machinery of Indian law. Its working content, in the form examinations expect: research must rest on adequate laboratory and animal work and a careful assessment of risks against anticipated benefits; the protocol must be submitted to an independent research ethics committee before the study begins; the interests of the participant prevail over those of science and society; special protection is owed to vulnerable groups; informed consent, preferably written, is required, with defined arrangements for those unable to consent; the placebo position of section 2.9 is stated here; participants injured by research are entitled to treatment and compensation; and results, negative as well as positive, must be made publicly available, with authors and sponsors accountable for publication ethics. The Declaration is not a statute, and its force is a teaching point in itself: it binds because regulators, journals, committees and courts treat it as the standard of the profession.

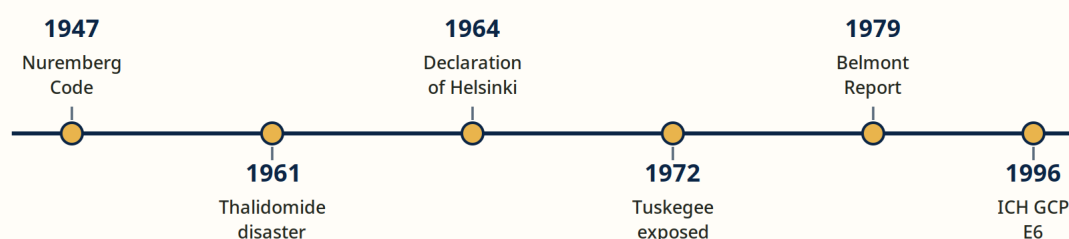
2.7 The origin of ICH GCP

The modern guideline grew from convergence. By the 1980s the Declaration, national rules and drug law each governed part of the field, and industry faced three regional systems (the United States, Europe and Japan) with diverging expectations for trial conduct and data acceptability. The International Conference on Harmonisation, founded in 1990 by the regulators and industry associations of the three regions, took up good clinical practice as an efficacy topic, and the result, **ICH E6**, the Guideline for Good Clinical Practice, was finalised in 1996: one ethical and scientific quality standard for designing, conducting, recording and reporting trials, built so that data generated under it would be accepted across regions and so that the rights, safety and well being of participants and the credibility of data were protected by the same

instrument. E6 codified what the history had taught, committee review, informed consent, qualified investigators, monitored conduct, auditable records, into an operating manual, and Unit 4 takes up its working content. Its revisions tell the same story in miniature: an integrated addendum, E6(R2), in 2016 added risk based quality management for the electronic age, and a third revision, E6(R3), adopted by ICH in 2025, re states the principles for decentralised and data rich trials.

Year	Instrument or event	What it added
1947	Nuremberg Code	Voluntary consent as the first principle
1961 to 1962	Thalidomide disaster and Kefauver Harris Amendments	Effectiveness evidence and premarket safety rigour in the USA
1964	Declaration of Helsinki	The physician's research code; committee review of protocols
1972 to 1979	Tuskegee exposed; Belmont Report	Justice, beneficence, respect for persons as the organising principles
1996	ICH E6 GCP	One conduct standard accepted across the ICH regions

How the Ethics Codes Were Written: 1947 to 1996



Each instrument answered the failure before it; GCP made the answers one standard

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Figure: The ethics timeline: Nuremberg, thalidomide, Helsinki, Tuskegee, Belmont and the arrival of ICH GCP, the instruments of sections 2.2 to 2.7.

2.8 The ethics of randomized clinical trials

Randomisation is scientifically natural and morally in need of defence, and the defence has a name: **equipoise**, the state of genuine uncertainty within the expert community about which of the compared treatments is preferable. While equipoise holds, allocating participants by chance deprives no one of a known better treatment, and the trial is the honest response to shared ignorance. When credible evidence destroys equipoise, continuing to randomise becomes unethical, which is why interim monitoring (section 2.13) is an ethical duty and not a statistical luxury. The standard objections are answered in kind: the doctor's duty to the individual patient is real but cannot rest on a preference that evidence does not support, and consent (section 2.15) is what makes the participant a partner in the uncertainty rather than a subject of it. Randomisation also carries the justice principle inside it: allocation by lot is the fairest known way to distribute the burdens of an uncertain comparison.

2.9 The role of placebo

A **placebo control**, an inert treatment indistinguishable from the test product, is the cleanest instrument for isolating a drug's effect, and the sharpest ethical edge in trial design, because the placebo participant is denied active treatment by design. The settled position, stated in the Declaration of Helsinki and worked out in ICH E10 (Unit 4), is a graded one. Placebo is acceptable where **no proven intervention exists** for the condition. It can also be acceptable where a proven intervention exists, only for compelling and scientifically

sound methodological reasons and where participants who receive placebo will not be exposed to additional risk of serious or irreversible harm: short periods, minor conditions, add on designs in which every participant receives standard therapy and the placebo replaces only the experimental addition, and rescue medication arrangements are the practical forms this takes. It is not acceptable where withholding treatment risks death or irreversible injury and the trial could have been designed otherwise. An examination answer on placebo states the two permitted cases and the harm limit; an answer that calls placebo always ethical, or never, has missed the doctrine.

2.10 Ethics of clinical research in special populations

The syllabus's phrase **special populations** names those whose consent is compromised, whose risk is asymmetric, or whose exploitation history demands structural protection: children, pregnant and nursing women, the elderly and frail, persons with mental illness or cognitive impairment, the unconscious, prisoners, students and employees in dependent relationships, and the poor and illiterate for whom payment can become coercion. The doctrine across all instruments is uniform in shape: inclusion must be scientifically necessary (the research cannot be answered in a less vulnerable group); risk is capped more strictly as capacity falls, for children, to minimal risk or a minor increase over it where there is no direct benefit; consent is layered, parental or legally authorised representative permission plus the child's own assent where the child can give it; and additional safeguards, independent monitors, community consultation, heightened committee scrutiny, are imposed by rule rather than left to goodwill. Exclusion is not the safe alternative it appears: populations excluded from research are later treated with drugs untested in them, which is why modern guidance presses for justified inclusion of women, the elderly (ICH E7) and children (ICH E11) rather than blanket protection by absence.

2.11 The ethics committee: IRB, IEC and Ethics Committee

Three names name one institution. **Institutional Review Board** is the American term of the federal regulations; **Independent Ethics Committee** is the ICH GCP term, emphasising independence from the institution conducting the trial; **Ethics Committee** is the term of Indian law. A regulatory writer must use the term of the document's jurisdiction and know they are the same safeguard: the independent, multidisciplinary body that reviews and approves the protocol, the consent documents and the site before the trial, and keeps the trial under review while it runs. Composition is prescribed because independence is structural, not attitudinal. Under the Indian NDCT Rules 2019 an ethics committee for clinical trials has **at least seven members**, drawn from medical, non medical, scientific and non scientific areas, and must include, in substance: a chairperson from outside the institution, a member secretary, a basic medical scientist (preferably a pharmacologist), a clinician, a legal expert, a social scientist or representative of a voluntary agency or philosopher or ethicist, and a lay person from the community, with adequate representation of age and gender and at least half of the members from outside the institution in the pattern ICMR guidance describes; a quorum, conventionally five members including specified categories, must be present for a decision. The United States federal regulations set their own floor of at least five members with scientific, non scientific and unaffiliated representation. Committees that will review clinical trials in India must be **registered**: ethics committees for clinical trials and bioavailability or bioequivalence studies with the Central Licensing Authority under the NDCT Rules, and ethics committees for other biomedical and health research with the designated authority in the Department of Health Research under the ICMR framework of Unit 4. An unregistered committee's approval is, for a regulated trial, no approval at all.

Ethics Committee Composition: Who Must Sit at the Table

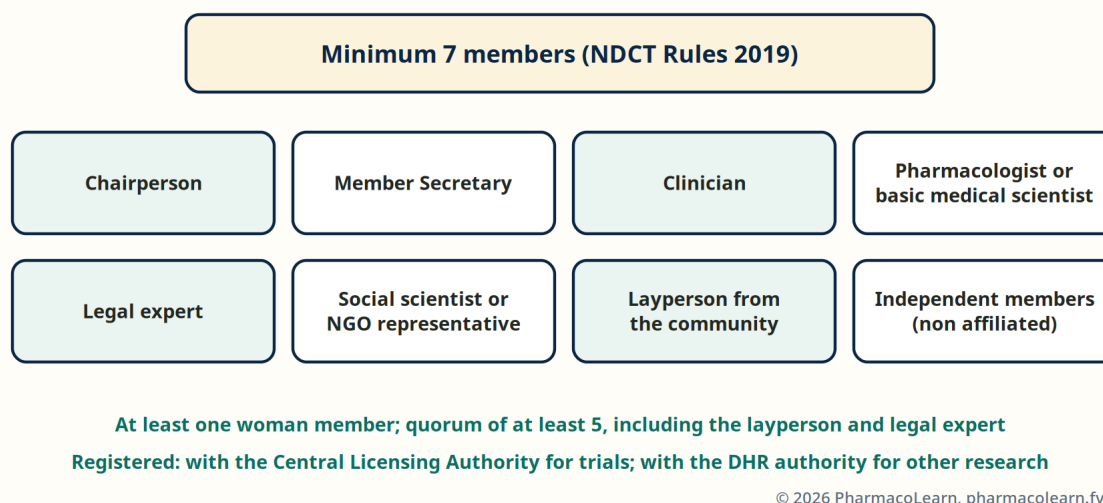


Figure: Ethics committee composition: the minimum seven members, the quorum rule and the two registration routes for trial and non trial research (Unit 2, section 2.11).

2.12 Committee work: review, approval and ongoing monitoring

The committee's product is decisions, in a defined order. **Initial review** examines the protocol for scientific validity (a badly designed study is unethical because it exposes participants to risk for no knowledge), for risk benefit balance, for fair participant selection, for the consent process and documents, for compensation and treatment arrangements for trial related injury, for the qualifications of the investigator and the site, and for the financial and insurance arrangements behind the trial. The outcomes are approval, approval after modification, or disapproval, recorded with reasons, with the committee's standard operating procedures governing voting, quorum, expedited review of minor changes and the handling of conflicts of interest among its own members. Approval is not the end of the committee's work: **ongoing monitoring of safety data** is the syllabus's own phrase for the continuing half of the mandate, comprising continuing review at defined intervals, review of amendments before implementation, prompt review of serious adverse events and of the sponsor's safety reports, review of protocol deviations, the power to require changes, to suspend or to terminate approval, and the site visits and audits some committees conduct. A committee that approves and sleeps has performed half its function, and inspection findings against sponsors and sites frequently begin exactly there.

2.13 Data safety monitoring boards

Some trials need a second, specialised guardian. A **data safety monitoring board (DSMB)**, also called a data monitoring committee, is an independent group of clinical, statistical and sometimes ethical experts, appointed by the sponsor but firewalled from the trial team, which alone has access to unblinded interim results and reviews accumulating safety and efficacy data while the trial runs. Its charter, written before the trial starts, states its membership, meeting rhythm, the data it will see, the statistical guidelines it will judge by, and its advisory powers: continue unchanged, continue with modification, or recommend stopping, for benefit so clear that equipoise (section 2.8) has ended, for harm, or for futility where the trial can no longer answer its question. The board is standard in large, long, blinded, multicentre and mortality endpoint trials, and its independence is its entire value: the sponsor learns the board's recommendation, not its data, so commercial hope cannot argue with the interim numbers. Regulatory guidance treats the DSMB as part of the trial's safety architecture, and the committee of section 2.11 receives its outcome reports as part of ongoing monitoring.

2.14 Responsibilities of sponsor, CRO and investigator

Ethical conduct is distributed, and the syllabus assigns the shares. The **sponsor**, the company or institution that initiates and finances the trial, carries ultimate responsibility for the trial's ethical and scientific integrity: appointing qualified investigators, obtaining regulatory and committee approvals, supplying a quality investigational product, monitoring conduct, reporting safety information, compensating trial related injury as the rules require, and insuring the trial. A **contract research organisation** (CRO) performs duties the sponsor transfers to it in writing, trial management, monitoring, data handling, but the transfer moves the task, not the accountability: the sponsor remains responsible for the quality and integrity of the trial. The **investigator**, the physician at the site, holds the duties no contract can move: protecting the rights, safety and well being of the participants in their care, conducting the trial exactly as the approved protocol directs, obtaining informed consent properly, keeping accurate records, and reporting adverse events on the clocks the protocol and the rules prescribe.

How a study earns the right to enrol its first participant
Protocol and investigator's brochure written and justified

- > Sponsor applies: regulatory permission where required (Unit 3)
- > Ethics committee: independent review, approval in writing
- > Consent documents approved as part of the same review
- > Site initiated only after both approvals are in hand
- > During the trial: committee continues review, DSMB watches unblinded data where appointed, sponsor monitors the site
- > Any serious breach or new risk: committee and regulator can suspend the study; the approvals are licences held on trust

2.15 Informed consent: principles, documents and process

Everything in this unit converges here. **Informed consent** is the process by which a competent person, given understandable information about a proposed study, freely decides whether to take part, and the signature is the evidence of the process, not the process itself. The governing principles descend from Nuremberg's first point through Belmont's respect for persons: consent must be **informed** (the information of the next paragraph, in language the participant actually understands), **comprehended** (checked, not presumed), **voluntary** (free of coercion and undue inducement, with the right to refuse or withdraw at any time without penalty or loss of entitled care), and **documented**. The two documents the syllabus names divide the labour. The **Patient Information Sheet** (participant information sheet) carries the information: the study's purpose and design, what participation involves visit by visit, the foreseeable risks and discomforts, the expected benefits and their uncertainty, the alternative treatments, the confidentiality arrangements and who may inspect records, the treatment and compensation available if injury occurs, the voluntary nature of participation, whom to contact, and the trial's registration identifier. The **Informed Consent Form** is the signed record that the information was given and the decision made, by the participant or, where the law permits and capacity is absent, by a legally authorised representative, with an impartial witness where the participant cannot read, and, in the Indian framework, with audio visual recording of the consent process in the circumstances the NDCT Rules prescribe. Three practical doctrines complete the section: consent is taken **before** any study procedure, including screening performed for the study; consent is **renewed** when new information emerges that could change the decision, through amended documents and re consent of those already enrolled; and the investigator who delegates the consent discussion remains responsible for its quality. A trial with defective consent is not a trial with a filing error: its data are ethically unusable, and regulators have refused applications on exactly that ground.

Informed Consent: What the Participant Must Be Told

The information (in the PIS)

Purpose, design and procedures
Foreseeable risks and discomforts
Expected benefits, and uncertainty
Alternative treatments available
Confidentiality and record access

The protections (in both documents)

Injury: treatment and compensation
Voluntary: refuse or withdraw freely
Contacts: investigator and committee
PIS carries the information
ICF records the signed decision

Informed, comprehended, voluntary, documented: in that order

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Figure: Informed consent: the information carried by the Patient Information Sheet and the protections the consent process guarantees (Unit 2, section 2.15).

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