PharmacoLearn

MPL204T Clinical Research and Pharmacovigilance, M.Pharm Semester 2

Unit 6: Pharmacoepidemiology, Pharmacoeconomics and Safety Pharmacology

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6.1 Pharmacoepidemiology: definition and scope

Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people: the application of epidemiological methods and reasoning to pharmacology's questions. Clinical trials establish that a drug can work and is acceptably safe in selected patients over months; pharmacoepidemiology establishes what the drug actually does in the population that receives it: the elderly and the pregnant, patients with five diseases and ten medicines, users who take half the dose or twice it, over years. Its scope covers beneficial and adverse effects alike, patterns and determinants of drug use, the effectiveness of risk minimization measures, and the quantification of risks that trials could only suspect. In the architecture of this subject it is the measurement science that Units 4 and 5 presuppose: spontaneous reporting detects, pharmacoepidemiology counts.

6.2 Study designs and data sources in pharmacoepidemiology

The designs are those of Unit 2 deployed at population scale: cohort studies in databases of millions, case control studies for the rarest outcomes, cross sectional drug utilization studies, and self controlled designs in which each patient is his or her own control across exposed and unexposed periods, cancelling fixed personal characteristics by construction. The distinctive craft is the data. Pharmacoepidemiology runs on **secondary data**: health insurance and health system claims, electronic health records, prescription and dispensing databases, disease and product registries, and the spontaneous report databases of Unit 5 read analytically. Working in such data demands its characteristic cautions: exposure is inferred from prescribing or dispensing, not observed ingestion; diagnoses are coded for billing as much as for truth; and **confounding by indication**, the disease causing both the prescription and the outcome, haunts every comparison and is fought with comparator choice, statistical adjustment and design. The discipline's credibility rests on naming these weaknesses and engineering against them, not on the size of the database.

6.3 What pharmacoepidemiology adds

Four contributions justify the discipline's place in this subject. **Rare and delayed effects**: only population scale sees the one in fifty thousand reaction and the cancer that follows a decade of exposure. **Real populations**: effects in pregnancy, childhood, old age and multimorbidity, the patients trials exclude, are measurable here and nowhere else. **Comparative safety**: drugs for the same disease can be compared head to head in use, answering the prescriber's actual question, which of these is safest, which trials rarely ask directly. **Drug utilization and policy**: who receives what, in what dose, for how long, and at what cost, evidence on which formularies, guidelines and safety interventions are built, and against which their success is judged. A pharmacovigilance system without pharmacoepidemiology can worry precisely; with it, it can also know.

6.4 Pharmacoeconomics: definition and the costs and outcomes frame

Pharmacoeconomics evaluates the costs and the consequences of pharmaceutical products and services, and asks the question scarcity forces: given that resources spent on one drug are unavailable for

everything else, which use of them buys the most health? Its frame is an equation with costs on one side, all of them, not only the drug's price but administration, monitoring, treating adverse effects and the costs of treatment failure, set against consequences on the other, measured in the units the next section distinguishes. The perspective of the analysis, patient, hospital, payer or society, decides which costs count, and must be declared before results mean anything. Pharmacoeconomics sits in this subject because safety is one of its inputs: an adverse reaction is simultaneously a clinical event, a pharmacovigilance case and an economic cost, and several historic withdrawals were, in effect, judgements that a drug's harm made its cost per unit of health unacceptable.

6.5 Types of pharmacoeconomic evaluation

Type	Costs measured in	Outcomes measured in	The question it answers
Cost minimization analysis (CMA)	Money	Assumed or proven equivalent	Outcomes are equal; which option costs least?
Cost effectiveness analysis (CEA)	Money	Natural clinical units: life years gained, blood pressure reduced, cases prevented	What is the cost per unit of effect?
Cost benefit analysis (CBA)	Money	Money	Do the benefits, valued in money, exceed the costs?
Cost utility analysis (CUA)	Money	Utility: quality adjusted life years (QALYs)	What is the cost per QALY, allowing comparison across diseases?

The four share one discipline: an **incremental** comparison, the extra cost of the newer option divided by its extra effect, since decisions are always between alternatives, never against nothing. Cost utility analysis, through the QALY, which weights years of life by the quality of health in which they are lived, supplies the common currency in which health technology assessment bodies compare a cancer drug with a vaccine programme, and its ratios inform, without mechanically deciding, reimbursement and formulary judgements. The examiner's expectation is the table's logic: identify what each type measures outcomes in, and the rest follows.

6.6 Safety pharmacology: definition and purpose

Safety pharmacology is the preclinical discipline that studies the undesirable pharmacodynamic effects of a substance on physiological functions, the functional safety counterpart to toxicology's structural focus. Where a toxicity study asks what a compound damages, a safety pharmacology study asks what it disturbs: does it prolong cardiac repolarization, depress respiration, alter behaviour or coordination, at exposures near the therapeutic one? Its regulatory frame is the ICH safety guidelines S7A, which organizes the field, and S7B, which addresses delayed ventricular repolarization, the QT interval, the mechanism behind the hERG channel story told across modern drug regulation, in which several marketed drugs were withdrawn for provoking a lethal arrhythmia. Safety pharmacology studies are performed before and alongside first human exposure precisely so that the functional hazards they detect can be designed out, monitored for in Phase I, or used to set stopping rules, linking this closing topic back to the trial safety monitoring of Unit 3.

6.7 The safety pharmacology core battery

ICH S7A defines a **core battery** of organ systems whose functions must be investigated, chosen because their acute disturbance can be life threatening:

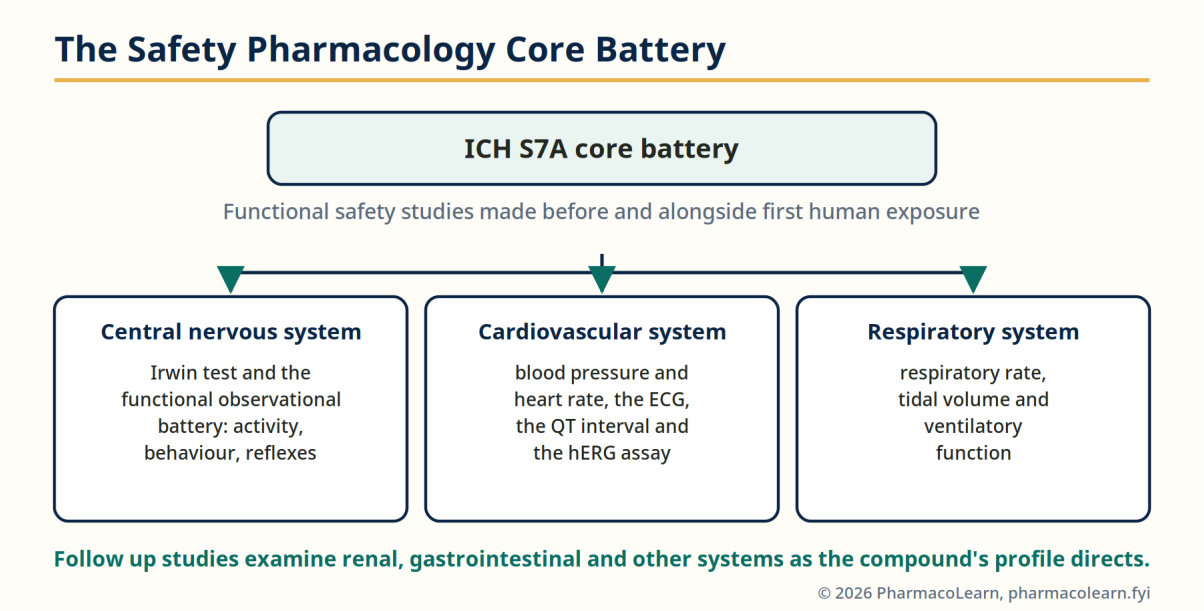

Figure: The ICH S7A core battery: central nervous, cardiovascular and respiratory function, the systems whose acute disturbance endangers life.

Central nervous system: motor activity, behaviour, coordination, reflexes and body temperature, screened by a functional observational battery or Irwin test in rodents. **Cardiovascular system**: blood pressure, heart rate and the electrocardiogram, with the QT interval and the in vitro hERG potassium channel assay at the battery's centre, since repolarization liability is the classic programme killing finding. **Respiratory system**: respiratory rate and measures of ventilatory function such as tidal volume. Beyond the core battery, **follow up and supplemental studies** examine systems as the compound's profile directs: renal and urinary function, gastrointestinal motility, autonomic and skeletal muscle endpoints, and deeper studies of any core system where a signal appeared. The closing symmetry of the subject is now visible: safety pharmacology watches function before the first volunteer is dosed, trial safety monitoring watches patients while evidence is built, and pharmacovigilance watches the world thereafter; one vigilance, three stations.

Frequently Asked Questions

Q: What is the difference between ICH-GCP and the Indian GCP guidelines? They are a standard and its national adaptation. ICH E6, adopted in 1996, is the international good clinical practice guideline written by the regulators and industry of the founding ICH regions, and it supplies the thirteen principles and the role definitions used worldwide. The CDSCO GCP guidelines of 2001 restate that standard for Indian law and institutions. An Indian trial satisfies both at once: the international guideline for scientific and ethical quality, the Indian documents and the governing statute for legal validity.

Q: An ethics committee approves a trial. Does the investigator still need regulatory permission? Yes, the two approvals answer different questions. The ethics committee judges the trial ethically: risk and benefit, consent, protection of participants. The regulator, in India the Central Licensing Authority under the New Drugs and Clinical Trials Rules 2019, grants legal permission to conduct the trial and import or manufacture the investigational product. Both must be in place before enrolment, along with the consent of each participant, which is a third, personal, approval.

Q: Severity and seriousness sound identical. How are they kept apart? By what each measures. Severity is intensity, graded mild, moderate or severe: how strong the event is. Seriousness is a regulatory category fixed by outcome: death, life threatening event, hospitalisation, disability, congenital anomaly, or other medical importance. A severe migraine is intense and non serious; a mild rash that requires

hospitalisation for observation is serious. Reporting clocks, compensation and regulatory attention follow seriousness, so the distinction is operational, not pedantic.

Q: Why is the case control study the classic design for studying rare adverse reactions? Because it starts from the outcome. A rare reaction affecting one user in fifty thousand would need an impossibly large cohort or trial to accumulate cases going forward, but the cases already exist in hospitals and records. Assembling those cases and matched controls and comparing past exposure gives an odds ratio efficiently and quickly, which is why historic reactions, from thalidomide embryopathy onward, were established by case based reasoning, at the price of depending on the quality of exposure history.

Q: Spontaneous reporting has no denominator and massive under reporting. Why does every country still build its pharmacovigilance on it? Because nothing else sees everything. It covers all drugs, all patients, all durations, at low cost, for the product's whole life, and it is exquisitely sensitive to the rare, unexpected and bizarre, exactly the reactions trials miss. Its weaknesses mean it generates hypotheses rather than rates, which is a proper division of labour: spontaneous reports raise signals, and the observational and targeted studies of Units 5 and 6 measure them. A system is not weak because its first instrument is a detector rather than a scale.

Q: WHO-UMC categories and the Naranjo scale both assess causality. Why two instruments? They trade precision differently. The WHO-UMC system gives qualitative categories, certain down to unassessable, judged on timing, dechallenge, rechallenge and alternatives, and is the language of national centres and pooled databases because it is fast and robust across millions of cases. The Naranjo scale scores ten explicit questions into definite, probable, possible or doubtful, which makes individual judgements reproducible and teachable, and suits hospital committees and publication. Both impose the same underlying logic; they differ in granularity and setting, and mature centres use each where it fits.

Q: Argus, Aris G and VigiFlow are all safety software. Who uses which? Argus (Oracle) and Aris G (ArisGlobal) are commercial safety databases used mainly by pharmaceutical companies and contract research organizations to process their case reports, meet expedited reporting clocks and submit electronically to regulators. VigiFlow is the Uppsala Monitoring Centre's web based system provided to national pharmacovigilance centres, through which their cases are managed and passed into the WHO global database, VigiBase. Same craft, different seats: industry systems face regulators, the national system faces the world pool.

Q: What is a signal, and is a statistical signal the same thing? A signal is information from one or more sources suggesting a new potentially causal association between a drug and an event, or a new aspect of a known association, judged likely enough to justify verificatory action. A statistical signal of disproportionate reporting is narrower: one detection method's output, showing a drug event pair reported more than background expectation. It is evidence towards a signal, not the signal itself, because disproportionality can be manufactured by publicity and reporting habits; the signal is declared only after the underlying cases are read and hold up.

Q: What does the safety pharmacology core battery cover, and why those three systems? The ICH S7A core battery covers central nervous, cardiovascular and respiratory function. These systems are chosen because their acute pharmacological disturbance can kill quickly: a seizure or profound sedation, a QT prolongation degenerating into a fatal arrhythmia, respiratory depression. They are therefore studied functionally before first human exposure, with follow up studies on renal, gastrointestinal and other systems as the compound's profile requires, so that Phase I monitoring and stopping rules can be built around known liabilities.

Q: Pharmacoeconomics is about money. Why does it sit in a pharmacology subject about safety?
Because value judgements decide which drugs populations actually receive, and safety is priced into them. Every adverse reaction carries costs, of treatment, hospitalisation and lost health, and cost utility analysis comparing cost per QALY will rank a safer drug above an equally effective but more toxic one. Formulary and reimbursement decisions made on pharmacoeconomic grounds are, in practice, safety decisions taken at population level, and a pharmacologist who cannot read them cannot follow where the subject's evidence finally acts.

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