



The WHO-ISoP Pharmacovigilance Curriculum: 2026 Update

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Abstract

This article presents a pharmacovigilance (PV) curriculum which was jointly developed by the World Health Organization (WHO) and the International Society of Pharmacovigilance (ISoP). It is an expanded update of a PV curriculum which WHO and ISoP developed in 2014 and responds to major scientific, technological, regulatory, social and public health developments that have reshaped PV over the last 12 years. Topics such as advanced therapies, global health emergencies, antimicrobial resistance, digital health, artificial intelligence, real-world evidence, medical device safety, the environmental impact of medicines, risk communication and patient engagement are addressed. The curriculum was developed through an international collaboration involving 82 contributors from different regions and professional backgrounds. The original three-level hierarchical structure was retained, with each chapter divided into four sections and each section into five or six subsections. The number of chapters increased from 15 to 26, the number of practical tasks from 40 to 125 and the number of references from 260 to 469. Practical tasks and references are provided as Electronic Supplementary Materials. The curriculum provides a comprehensive and structured inventory of contemporary PV and thus represents a reference that lecturers and institutions can use to develop context-specific training programmes. Its structure provides conceptual clarity while allowing adaptation to different settings, learners' roles and prior knowledge, local priorities, available time and resources. It is not intended to prescribe a single standardised course. Instead, it supports the development of introductory, advanced, comprehensive or topic-specific PV education programmes. The update reflects a shared commitment of the WHO and the ISoP to strengthening PV education and capacity across regulatory, academic, healthcare, public health and industrial settings in accordance with the recommendation of the 2026 World Health Assembly to strengthen PV.

1 Introduction

1.1 Background

The World Health Organization (WHO) defines pharmacovigilance (PV) as 'the science and activities concerned with the detection, evaluation, understanding, and prevention of adverse effects or other problems associated with medicines and vaccines' (reference in Online Resource

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Key Points

This pharmacovigilance curriculum expands and updates the 2014 version and was developed by 82 contributors on behalf of WHO and ISoP.

It provides a symmetric three-level hierarchical inventory of PV, supported by practical tasks and relevant literature.

It can be used as a basis for PV courses adapted to various training objectives, audiences, regional needs and settings.

Annex II). This definition reflects the broad, multidisciplinary nature and responsibility of PV, which draws on fields such as clinical pharmacology, modern biochemical and information technologies, data science, pharmacoepidemiology, as well as regulation, communication and public health.

The use of the terms ‘detection’ and ‘prevention’ emphasises that PV has not only a reactive role—in the sense of identifying and analysing harm that has already occurred—but also a distinctly proactive one. Risk management begins already during the development of medical products, it continues through the promotion of appropriate prescribing practices and concludes with the correct implementation of therapeutic decisions.

Furthermore, pharmacoepidemiological and public health methods contribute to PV by estimating the severity, frequency, preventability, and population burden of medicine-related harm, including harm caused by common and well-recognised adverse drug reactions (ADRs).

The abovementioned functions of PV require in-depth knowledge of both drug-related hazards and the methods used to identify, measure and minimise them. Such competencies represent core knowledge and skills for practicing PV professionals. Nevertheless, the degree to which they must be mastered is highly context-dependent, and varies according to diverse factors including professional sector, practice setting, and level of decision-making authority.

A strong PV workforce which collectively possesses context-relevant core skills and capabilities is essential to advancing patient safety worldwide. Consequently, there has long been a significant and ever-growing demand for PV-focused training and capacity-building opportunities. To address this need, the WHO and the International Society of Pharmacovigilance (ISoP) jointly developed a comprehensive, systematically structured inventory of PV subject matter, the ‘WHO-ISoP PV Curriculum’, which was published in *Drug Safety* in 2014 [1].

This core curriculum was designed to support all stakeholders involved in the design and delivery of PV courses. It provides teachers with clarity regarding universally agreed core

competencies that should absolutely be imparted through any PV training programme, while simultaneously offering flexibility to select the topics most relevant to their learners’ needs and contexts and enrich teaching and learning with practical exercises and recommended literature, as appropriate. The curriculum was designed to be comprehensive, but not prescriptive; it could be covered in its entirety in programmes designed to provide exhaustive training (e.g. master’s degrees or equivalent courses), or adopted in a modular manner, focusing on specific sections or sub-sections for shorter, more targeted learning activities.

PV is a dynamic discipline that evolves with scientific, technological and social developments. As such, and as noted in the 2014 publication, the PV curriculum requires periodic revision. Over the past decade, these developments have been sufficiently substantial to warrant a comprehensive renewal and expansion of the original version. The updated PV curriculum presented in this article also aligns with the landmark recommendation of the 79th World Health Assembly 2026 to strengthen PV [2, 3].

1.2 Rationale for Updating the Curriculum

Since the publication of the 2014 WHO-ISoP curriculum, PV has undergone substantial transformation. Not only has the scope of the discipline expanded, but the competencies required of PV professionals have evolved. Below, we highlight several key developments that have contributed to the need for this update.

First, therapeutic innovations have accelerated significantly. The expanded adoption of Advanced Therapy Medicinal Products (ATMPs), alongside the increasing use of more complex biologics, drug device combination products and targeted treatments, has introduced new safety issues and long-term uncertainties. These developments require enhanced capabilities in risk characterisation, follow-up and multidisciplinary assessment.

Second, global health emergencies and an evolving risk landscape, most notably the COVID-19 pandemic, have brought into sharper focus the need for rapid signal detection, real time data generation, monitoring and integration and effective risk communication under conditions of multiple open questions, especially regarding adverse events following immunisation (AEFI). At the same time, the burden of difficult-to-manage adverse drug reactions (ADRs), antimicrobial resistance, opioid addiction, medication errors (MEs) and the increasing trade in substandard falsified medical products (SFMPs) have created new challenges for PV as a core component of patient safety systems.

Third, digital transformation and data science have reshaped healthcare as well as PV practice. The widespread use of electronic health records, mobile health technologies and social media has greatly expanded the data sources for safety monitoring. Concurrently, advances in real-world evidence generation, artificial intelligence (AI) and

data analytics have enabled more proactive and predictive approaches to signal detection and risk management. These developments require new competencies in data governance, validation and interpretation.

Fourth, health behaviour and communication have fundamentally changed. Patients and healthcare professionals (HCPs) now operate in an environment of rapid information exchange, in which misinformation may be amplified and selectively targeted through digital and social media algorithms, potentially influencing treatment adherence, medicine use and vaccine acceptance. This necessitates a stronger focus on risk communication, health literacy, implementation science and patient engagement as integral components of PV.

Fifth, the importance of environmental and societal considerations to PV has increased. Expanding medicine use and pharmaceutical production, improved detection of active pharmaceutical residues in the environment, concerns about antimicrobial resistance and ecological effects, as well as greater attention to the sustainability of healthcare have strengthened the field of ecopharmacovigilance (EcoPV). At the same time, fragmented health systems, polypharmacy, exposure to SFMPs and limited health literacy increasingly influence medicine-related risks and the capacity to identify and prevent harm.

These developments require well-trained PV professionals who can identify, assess, interpret, communicate and mitigate risks using robust, data-based methods and can take evidence and uncertainty into account when making decisions. They also require structured educational guidance to help trainers design courses that are current, relevant and adaptable to different audiences and settings.

This updated curriculum, developed under the authority of WHO and the recognised global expertise of ISoP, is intended to provide such a structured reference framework.

2 Development of the New Curriculum

2.1 Old and New Topics and Sources

The curriculum is intended to serve as a framework for both introductory courses targeted to beginners in the field, and advanced programs for learners who already possess a certain level of understanding of PV but want to improve their knowledge and skills in specific areas. To address the former, it was deemed essential—as in the original curriculum—to include dedicated components on the fundamentals and history of PV, the significance of the discipline to public health and the PV of medicines that have been most widely used for decades, and their well-known, common ADRs which play a huge role for many people worldwide.

However, the emergence of important new topics over the past 12 years required substantial expansion of the 2014 version. Key sources informing the update included recent literature from the *Drug Safety* journal, particularly for emerging PV topics, and the *Pharmacoepidemiology and Drug Safety* journal for topics related to ADR frequency and epidemiology.

For regulatory content, guidelines from international organisations, in particular the WHO, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Council of International Organizations for Medical Sciences (CIOMS), the European Medicines Agency (EMA), as well as major national regulatory authorities, such as the US Food and Drug Administration (US FDA) were used. Additional emerging topics were identified through topic-specific journals and the agendas of relevant professional societies' conferences (e.g. the International Society for Pharmacoepidemiology).

2.2 Working Groups

The expanded scope of the updated curriculum, and the intention to strengthen global representation and to involve key WHO and ISoP working groups, resulted in a broader and more diverse group of expert co-authors. The number of contributors increased almost five-fold, from 18 to 82.

Experts were recruited from seven sources: authors of the original curriculum, WHO staff members, members of the WHO 'Advisory Committee on Safety of Medicinal Products', members of the WHO 'Global Advisory Committee on Vaccine Safety', chairpersons of ISoP Special Interest Groups (SIGs), members of the ISoP Scientific Board and other scientists recommended for their specific expertise. The contributors represented all continents and included experts from academia, regulatory authorities, industry, consulting firms and non-governmental organisations (NGOs).

The authors were assigned to chapter- or section-specific teams according to their areas of expertise. They received guidance on the required contributions, including the proposal and discussion of chapter, section and subsection titles, practical exercises and basic and specific references for further reading. A total of 62 working groups of different sizes were formed. Coordinators were appointed for medium and large groups (four to eight) to support harmonisation of the proposals.

Formal consensus methods, such as the Delphi process, were not needed, because working groups preferred to reach agreement through open discussion and coordination. Close cooperation between WHO and ISoP, as the curriculum sponsors, was essential throughout the process.

Table 1 Chapters, sections and subsections of the PV curriculum

Chapter 1: What Is Pharmacovigilance (PV) and Why Do We Need It?**1.1 Introduction to Pharmacovigilance (PV)****1.1.1 Key definitions in PV: adverse event (AE), adverse drug reaction (ADR), adverse event following immunisation (AEFI); HCP and MAH****1.1.2 Historical evolution of PV: from thalidomide to modern systems****1.1.3 Scope and subjects of PV: individual ADR cases, pharmacoepidemiology, molecular pharmacology and toxicology and public health (PH)****1.1.4 Stakeholders in PV: HealthCare Professionals (HCPs), patients, regulators, industry, academia and others****1.1.5 Key international bodies and PV initiatives: WHO, WHO PIDM, UMC, CIOMS, ISoP, ISPE and ICH****1.1.6 The international importance of PV owing to the relevance of locally detected medication risks to other parts of the world as well****1.2 Fundamental Uncertainties of Pharmacovigilance and their Reasons and Consequences****1.2.1 Why risks cannot reliably be predicted from drug development: not real world, too short or too few cases (rule of three)****1.2.2 Mostly, many more different ADRs than desirable effects, low ADR frequencies and limited information about the risks****1.2.3 Patient disposition as the big unknown: why do only few patients suffer from certain ADRs, and what makes them distinct?****1.2.4 Post-marketing data uncertainties: often passively collected post-exposure information. Active challenge not ethical****1.2.5 Heterogenous categories of harm data and criteria: biochemistry, clinics, therapeutic measures or outcomes; confounding problems****1.2.6 Patients' and HCPs' uncertainty and anxiety in view of limited knowledge about ADR-related risks: actions guided by precaution****1.3 Mission, Objectives and Challenges of Pharmacovigilance****1.3.1 Prevention of immediate harm to individual patients through their carers' knowledge, attention and decisions****1.3.2 Early detection of previously unrecognised ADRs****1.3.3 Risk assessment and Benefit-Risk (B-R) evaluation of medicines****1.3.4 Development of safe medicines and promotion of their rational and safe use****1.3.5 Transparent communication about risks associated with the use of medicines****1.3.6 Contribution to regulatory decision-making****1.4 Why Pharmacovigilance is Essential for Public Health (PH)****1.4.1 Reducing morbidity and suffering of patients and healthcare costs owing to ADRs****1.4.2 Addressing and reducing risks in vulnerable populations (e.g. children, elderly and pregnant women)****1.4.3 Monitoring safety of well-known and new health products, incl. vaccines, herbal and traditional medicines and biological products****1.4.4 Raising alarm in case of emerging worldwide medication problems, e.g. unsafe manufacturing or utilisation of certain medicines****1.4.5 Contribution of PV in global health emergencies (e.g. risk assessment, quantification, communication of COVID-19 vaccines)****1.4.6 Detection of rare, long-term ADRs, misuse, abuse, medication errors and other drug-related problems in real-world drug utilisation****Chapter 2: Fundamental Molecular and Clinical Aspects of Adverse Drug Reactions and Adverse Events Following Immunisation****2.1 Types and Mechanisms of ADRs and Vaccine Product-Related AEFI****2.1.1 Intrinsic potential (reactogenicity) of drugs to cause ADRs and of vaccines to cause product-related AEFI****2.1.2 Manifestation of this potential in the causation of individual cases: vaccine product-related AEFI, ADRs caused by other drugs****2.1.3 Types of ADRs and vaccine product-related AEFI: type A (predictable from drug's pharmacology), type B (idiosyncratic/allergic)****2.1.4 Other types of ADRs: C (chronic), E (end of use) and F (failure); AESI (vaccine product-related Adverse Events of Special Interest)****2.1.5 Classification of ADRs according to 'DoTS' (dose, time course and relevant susceptibility) and to 'EIDOS' (mechanistic)****2.1.6 Morphologic, chemical, physical, functional, perceptual, psychological ADRs and product-related AEFI****2.2 Development Over Time, Severity and Consequences for Affected Patients, Measurement Parameters****2.2.1 Hazard function of ADR/AEFI appearance: time independent, early onset, intermediate, cumulative, delayed and end of treatment****2.2.2 Asymptomatic precursors (surrogate markers) and chemical/physical lab data of ADRs and vaccine product-related AEFI**

Table 1 (continued)

2.2.3 Direct clinical or lab measurement of severity versus indirect measurement based on complications or necessary actions ('proxies')
2.2.4 Impaired quality of life as ADR/AEFI-related harm; components and measurement. Harm quantification in litigation and claims
2.2.5 Type of variable of the severity of ADRs/AEFI: continuous (e.g. diarrhea; quantifiable) versus binary (bone fractures; countable)
2.2.6 Severity, seriousness, scales, maxima and deliberate dichotomisation (cut-off) for practical reasons: ADR reporting or counting
2.3 Frequency of ADRs
2.3.1 Limited and varying diagnostic certainty and causality of ADRs/AEFI; consequence for counting, reporting and impact assessment
2.3.2 ADR/AEFI number related to population, treated patients, treatment episodes, treatment time and patient-years
2.3.3 Prevalence, incidence, incidence density; number needed to harm (NNH), morbidity and case fatality rate
2.3.4 Requirements for size of safety database for drugs, vaccines at application for licensure and labelling. 'Rule of three'
2.3.5 Post marketing challenges: estimation patient exposure (doses distributed/sold versus administered); source: relevant MAH and CRO
2.3.6 Frequency classes, established terms in product labelling: very common, common, occasionally, rare and very rare
2.4 Clinical Management of ADRs and Suspected Vaccine Product-Related AEFI
2.4.1 Patient-level a priori risk assessment, precautionary measures
2.4.2 Causality Assessment if ADR suspected (see Chapter 14)
2.4.3 Treating symptoms of ADRs
2.4.4 Adjusting treatment after ADR occurred, e.g. dose reduction, treatment/prevention of ADR and alternative medicines
2.4.5 Patient observation after dose reduction or treatment termination and possibly resumption of medication ('de- and rechallenge')
Chapter 3: Selected Important ADRs and AEFI
3.1(1-3) Drug-Induced Liver Injury (DILI)
3.1.1 DILI and Herb-Induced Liver Injury (HILI): definition, classification and phenotypes. Epidemiology: incidence and risk factors
3.1.2 DILI signals in clinical trials and post-marketing setting (case reports, registries); applying Hy's law
3.1.3 Monitoring and evaluating liver toxicity of drugs: anti-cancer-, TB- and antiretroviral therapies; assessing AE causality
3.1(4-6) Acute Kidney Injury (AKI)
3.1.4 Characterisation of AKI: definition, mechanism, severity (from mild creatinine rise to renal replacement therapy), reversibility
3.1.5 Other renal ADRs: pseudo-AKI. Non-AKI ADR (albuminuria, haematuria, pyuria); idiosyncratic Type B vs. dose-dependent Type A ADRs
3.1.6 At-risk populations for AKI: critically ill subjects, elderly, high comorbidity, polypharmacy and chronic kidney disease
3.2(1-3) Heart Rhythm Disorders, QT Prolongation
3.2.1 QT-prolongation: definition, mechanism, risk factors, drugs prolonging QT and their synergism; risk of torsades de pointes
3.2.2 Specific drug-induced other arrhythmias: brady-arrhythmias, AV-block, atrial fibrillation and unmasking Brugada syndrome
3.2.3 Drug-induced electrolyte imbalances and their impact on heart function: increased or decreased serum K, Mg and Ca
3.2(4-6) Nervous System Disorders
3.2.4 Cranial neuropathy: vision, smell, taste, hearing disorders, vertigo. Peripheral: sensory, motor and sexual function disorders
3.2.5 Seizures in patients with/without epilepsy; headache, delirium, coma, GBS, tardive dyskinesia, parkinsonism, myasthenia and PML
3.2.6 Psychiatric disorders: confusion, agitation, mental inhibition, depression, mania, sleep disorders, cognitive changes and psychoses
3.3 Blood Dyscrasias
3.3.1 Red blood cell disorders: anaemia, red cell aplasia, methemoglobinemia and haemolytic anaemia
3.3.2 White blood cell disorders: febrile neutropenia, leukopenia, agranulocytosis (clozapine, metamizole), leucocytosis and eosinophilia
3.3.3 Platelet disorders: thrombocytopenia (heparin, rifampicin), purpuras, thrombocytosis, hypercoagulability and hypoprothrombinaemia
3.3.4 Bone marrow disorders: pancytopenia (chemotherapy), hypocellular bone marrow and myelodysplasia
3.3.5 Others: microangiopathic syndromes, acute leukaemia, disseminated intravascular coagulation (DIC), haemolytic uremic syndrome

Table 1 (continued)

3.4 Skin Disorders (for urticaria/anaphylaxis see Section 5.1.2)
3.4.1 Erythematous exanthema (rash) and maculopapular eruption (T cell-mediated type IV reactions)
3.4.2 Photosensitivity: phototoxicity and photoallergy
3.4.3 Vasculitis: necroses, clinical severity, chronological development; histological diagnosis, epidemiology
3.4.4 Serious cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome, toxic epidermal necrolysis. Diagnosis, epidemiology
3.4.5 Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP); epidemiology
3.4.6 Chronic adverse cutaneous reactions: pigmentary changes, acne, pemphigus and lupus erythematosus
Chapter 4: Risk Factors, Patient-Related
4.1 Risks for the Elderly
4.1.1 Pharmacokinetics and pharmacodynamics in elderly patients
4.1.2 Comorbidities and polypharmacy
4.1.3 Frailty (muscle weakness, fatigue, clumsiness, forgetfulness) potentially enhanced by ADRs and causing medication errors (MEs)
4.1.4 Clinical trials and studies designed to capture ADR-related risks of elderly patients
4.1.5 Potentially inappropriate medications: Beers criteria, PRISCUS List, EU(7)-PIM, FORTA List. Minimisation of ME risks
4.1.6 Improving therapeutic adherence and reducing risks by adapting pharmaceutical forms and instructions for the elderly
4.2 Risks for Children
4.2.1 Introduction: how to develop a paediatric safety profile
4.2.2 Physiological aspects: developmental pharmacokinetics and pharmacodynamics in children, and effect on drug safety profiles
4.2.3 Risk factors and confounders of ADRs/AEFI in children, including formulation safety, off-label and unlicensed co-medications
4.2.4 ADRs, AEFI and MEs specific to children, risk management for children and specific education of carers
4.2.5 Methodology in studying drug safety in children: single case AE assessment and pharmacoepidemiology specific to children
4.2.6 Regulatory guidelines, informed consent in clinical trials, communicating benefit versus risk specific to children and carers
4.3 Risks for Women; Risks from Pregnancy and Breastfeeding
4.3.1 Specifically higher ADR risks in women compared to men: types of medicines and ADRs (for OCs and HRT see Sections 6.3.5–6.3.6)
4.3.2 Pharmacokinetic/dynamics changes and specific morbidity due to pregnancy (e.g. gestational diabetes) causing higher ADR risks
4.3.3 Risks to a newborn child owing to maternal drug exposure during the perinatal period or during the birth process (e.g. opioids)
4.3.4 Teratogenic risk classification: e.g. FDA A/B/C/D/X and PLLR (Pregnancy-Lactation Labeling Rule). Pre/post-conception advice
4.3.5 Medications that pass into breast milk and endanger the newborn (e.g. amiodarone, retinoids and opioids)
4.3.6 Regulatory, programmatic, ethical requirements for pharmacotherapy and PV for pregnant and breastfeeding women (WHO, EMA, FDA)
4.4 Patient Susceptibility to ADRs: Genetic Risks, Damaged Microbiome, Comorbidity and Other Risk Factors (see also Chapter 5)
4.4.1 Definition, scope and challenges of pharmacogenetics and pharmacogenomics (PGx); risks for patients
4.4.2 Genomic biomarkers of polymorphism of drug-metabolising enzymes and drug-transporting proteins
4.4.3 Genomic biomarkers of polymorphism of ion channels, receptors and enzymes involved in pharmacodynamics
4.4.4 Genomic biomarkers of polymorphism of genes responsible for immunological reactions, including against biologics and vaccines
4.4.5 Gut microbiome and ADRs
4.4.6 Conditions that alter susceptibility to ADRs/AEFI, including comorbidities
Chapter 5: Risk Factors, Exposure-Related
5.1 Previous Exposure to Drugs (Immune Reactions Types I-IV)
5.1.1 The basic immunology of the Gell–Coombs classification and clinical presentations incl. types I–type IV (with subtypes a–d)
5.1.2 Severe immediate ADRs and AEFI—anaphylaxis, including non-IgE-mediated (type I) mechanisms
5.1.3 Severe organ manifestations of immunological ADRs and AEFI: liver, kidney, lung, heart, blood vessels and blood cells (skin see 3.4)

Table 1 (continued)

5.1.4	Drugs causing frequent or severe immunological ADRs/AEFI: antibiotics, NSAIDs, antiepileptics, TK- and ACE inhibitors and vaccines
5.1.5	Clinical management of immunological ADRs and AEFI: diagnosis incl. laboratory test verification, treatment and precautionary measures
5.2	Pharmacokinetic Drug-Drug Interactions (DDI)
5.2.1	Absorption: altering gastrointestinal pH, motility, activity of transporters and modulation of intestinal P-glycoprotein (P-gp)
5.2.2	Distribution: competing for binding at plasma proteins and altering their concentration at drug transporters
5.2.3	Metabolism: CYP450: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4/A5; auto- and hetero-induction and inhibition
5.2.4	Excretion: altering renal blood flow or competing for renal transporters
5.2.5	Drug–drug interactions affecting different organs or patients with comorbidities or genetic polymorphism in drug metabolism
5.2.6	Drug interactions with food, alcohol, smoking and other environmental factors (see also Section 9.4(4-6))
5.3	Pharmacodynamic Drug-Drug Interactions (DDI)
5.3.1	Pharmacodynamic DDI, synergistic
5.3.2	Pharmacodynamic DDI, antagonistic
5.3.3	Pharmacodynamic DDI related to dosage or duration of treatment
5.3.4	Pharmacodynamic DDI related to timing of administration
5.3.5	Pharmacodynamic drug interactions with alcohol, food, food supplements and other environmental factors (incl. heat, radiation)
5.3.6	Drug interactions in patients with other risk factors, e.g. comorbidities or genetic polymorphisms affecting pharmacodynamics
5.4	Alcohol, Other Stimulant Well-Being Products; Solar Radiation, Heat, Stress
5.4.1	Pharmacokinetic and pharmacodynamic drug interactions with alcohol
5.4.2	Drug interactions with smoking
5.4.3	Drug interactions with illicit stimulant drugs, e.g. cocaine, GHB, MDMA and synthetic cathinones
5.4.4	Drug interactions with caffeine, including all caffeine-containing beverages such as coffee, black tea and protein coffee
5.4.5	Drug-induced photosensitivity: photoallergic and phototoxic reactions
5.4.6	Effects of climate change and heat on drug effects and effects of drugs on thermoregulation
Chapter 6: ADRs of Frequently Used Medicines	
6.1	Non-Opioid Analgesics
6.1.1	Aspirin: haemorrhage, GI bleeding, gastritis, haemorrhagic stroke, asthma, Reye's syndrome. Precaution before surgery!
6.1.2	Non-steroidal anti-inflammatory drugs (NSAIDs): GI-bleeding, renal, cardiovascular ADRs, serious cutaneous adverse reactions
6.1.3	COX-2 selective NSAIDs: GI advantage, but risk of cardiovascular ADRs (myocardial infarction, stroke)
6.1.4	Paracetamol: Severe DILI at overdose (>4g), long-term AKI. Metamizole: anaphylaxis, agranulocytosis
6.1.5	Combination analgesics (e.g. paracetamol or NSAIDs with opioids): constipation, respiratory depression due to opioid component
6.1.6	GABA analogues gabapentin, pregabalin (for neuralgic pain): dizziness, drowsiness, fatigue and ataxia. Pregabalin: misuse, abuse
6.2	Typical Medicines for the Elderly: Antihypertensives, Alpha 1-Adrenoceptor Blockers, Statins and Metformin
6.2.1	Main antihypertensives. ACE inhibitors: angioedema, cough; ARB: enhance K, Na; teratogenic; CCB: peripheral edema
6.2.2	Other antihypertensives. Diuretics lower K, Na and Mg; thiazides worsen gout and diabetes. Betablockers worsen asthma; abrupt stop risky
6.2.3	Alpha 1-adrenoceptor blockers for BPH. Tamsulosin, others. Main ADRs: hypotension, sexual dysfunction. Tamsulosin: floppy iris
6.2.4	Statins. Frequent ADRs: myalgia. Rare, serious ADRs: myopathy, rhabdomyolysis. Collectively: 'Statin-Associated Muscle Symptoms'
6.2.5	Metformin. Frequent ADRs: GI symptoms like stomach pain, nausea, diarrhea. Rare serious ADR: lactic acidosis
6.3	Proton Pump Inhibitors (PPIs), H2-Receptor Antagonists (H2RAs); Female Sexual Hormones
6.3.1	PPIs. Frequent ADRs: low Mg. rare serious ADRs: AKI (TIN), fractures, SCARs. Withdrawal: hypergastrinaemia
6.3.2	PPI-DDI: clopidogrel, digoxin, methotrexate, tacrolimus, phenytoin and antiretrovirals
6.3.3	H2RA ADRs: mental status change, vitamin B12 deficiency, DILI. Cimetidine: gynecomastia

Table 1 (continued)

6.3.4 H2RA, mainly cimetidine: DDI with CYP450-metabolised drugs (increasing the concentration), e.g. warfarin, theophylline and phenytoin
6.3.5 Oral contraceptives: various estrogens and gestagens, drug-drug and drug-device combinations. ADRs: mood swings, nausea, VTE and MI
6.3.6 Hormone replacement therapy: estrogen/progestin combinations. Rare serious ADRs: VTE, MI, stroke and carcinoma (uterus, breast)
6.4 Benzodiazepines, Z-Drugs, Selective Serotonin Reuptake Inhibitors (SSRIs)
6.4.1 Benzodiazepines. ADRs: CNS depression (drowsiness, confusion), long-term tolerance. Rare serious ADR: respiratory depression
6.4.2 Z-drugs (zolpidem, zopiclone etc.). ADRs: Complex Sleep Behaviors like sleepwalking; amnesia and falls
6.4.3 SSRIs. ADRs: gastrointestinal incl. bleeding, sexual dysfunction, insomnia, anxiety and weight change. Serious: serotonin syndrome
6.4.4 Overdose and intoxication from benzodiazepines, Z-drugs and SSRIs
6.4.5 Dependence and withdrawal syndrome
6.4.6 Strategies for minimising risks of ADRs with benzodiazepines, Z-drugs and SSRIs
Chapter 7: ADRs of New Important Drugs
7.1 ADRs of Monoclonal Antibodies (MABs) as Checkpoint-, TNF α - and IL-Inhibitors; ADRs of antibody-drug conjugates
7.1.1 MAB-ADRs: Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, acute anaphylaxis, serum sickness and SJS/TEN
7.1.2 MAB-ADRs: Anemia, leukopenia, thrombocytopenia, haemorrhages, intravascular haemolysis; opportunistic infections
7.1.3 MAB-ADRs: Gastrointestinal (GI) toxicities (rarely with angiogenesis inhibitors: GI perforation), DILI and pancreatitis
7.1.4 MAB-ADRs: Cardiovascular toxicities (cardiac arrhythmias including QT prolongation/TdP, heart failure and hypo- or hypertension)
7.1.5 MAB-ADRs: Other toxicities (infusion/injection site reactions, vascular toxicity, AKI, secondary malignancy and PML)
7.1.6 ADCs (often due to premature or off target cytotoxic payload release): blood-, neurological, pulmonary and GI ADRs
7.2: Tyrosine Kinase Inhibitors (TKi)
7.2.1 Cardiac ADRs: fluid retention with pleural and pericardial effusion, heart failure and hypertension. Rare myocardial infarction
7.2.2 Liver- and renal toxicity: hyperbilirubinemia, increased ALT/AST. AKI
7.2.3 GI disorders: stomach pain, diarrhea, nausea, anorexia, stomatitis and rare GI perforation
7.2.4 Blood dyscrasias: neutropenia, thrombocytopenia, anemia; bleeding incl. intratumoral bleeding
7.2.5 Skin toxicity: hand-foot skin reaction (HFSR), rash, mucositis, dry skin, pruritus and periungual tissue inflammation
7.2.6 Other: frequent headache, sleep disorders. Embryo-fetal toxicity (first trimester). Tumour lysis syndrome (TLS)
7.3 GLP1 Receptor Agonists (GLP1RA), Tirzepatid, Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i), Novel Oral Anticoagulants
7.3.1 GLP1RA-ADRs: nausea, vomiting, diarrhea, constipation and abdominal pain. Depression. Rare NAION
7.3.2 GLP1RA caution in frail elderly malnourished patients: sarcopenia, risk of falls and reduced quality of life
7.3.3 GIP/GLP1RA-ADRs: nausea, diarrhea. Rare serious: acute pancreatitis, anaphylaxis
7.3.4 SGLT2i (Glifozin)-ADRs: genitourinary infections, polyuria, volume depletion and hypotension. Rare serious: lower limb gangrene
7.3.5 Challenges in assessing risks from late and rare GLP1RA- and SGLT2i-ADRs, in particular RCT versus RWD, ITT versus PPA
7.3.6 NOAC-ADRs: Bleeding, GI-symptoms, rare allergic reactions. Mostly early onset (first week)
7.4: Chimeric Antigen Receptor T-Cell (CAR-T), T Cell Receptor (TCR-T) and Gene Therapy
7.4.1 CAR-T- and TCR-T-cell therapy: principles, manufacturing and applications
7.4.2 Cytokine release syndrome
7.4.3 Immune effector cell-associated neurotoxicity syndrome (ICANS)
7.4.4 Secondary malignancies
7.4.5 Other ADRs: blood cell count depression, infections and off-target organ toxicity
7.4.6 Risks of gene therapy: severe immune reactions, viral vector infection, 'off-target' organ toxicity and cancers
Chapter 8: ADRs of Anti-Infective Medicines (Including Vaccines) Used in Pandemic; Neglected Tropical and Emerging Infectious Diseases
8.1 Vaccine Product-Related AEFI of mRNA Vaccines and Adenoviral-Vectored Vaccines Used in SARS-Cov-2

Table 1 (continued)

8.1.1 Main risk: Myocarditis and pericarditis

8.1.2 Anaphylaxis

8.1.3 Vaccine-induced immune thrombotic thrombocytopenia (VITT), thrombosis with thrombocytopenia syndrome (TTS)

8.1.4 Acute peripheral facial palsy, tinnitus and heavy menstrual bleeding

8.1.5 Neuroinflammatory disorders: Guillain-Barré-Syndrome (GBS), transverse myelitis and acute disseminated encephalomyelitis

8.1.6 Other important AEFI with adenoviral-vectored covid-19 vaccines: immune thrombocytopenia, capillary leak syndrome

8.2 Other Important New Vaccines and Their Indications

8.2.1 Novel vaccine adjuvants including Matrix M, CpG-oligodeoxynucleotides: impact on innate immunity and implications for safety

8.2.2 Self-amplifying mRNA vaccines: design rationale and implications for safety, such as needs for long-term safety monitoring

8.2.3 DNA vaccines: design rationale and implications for safety, such as administration requirements; concerns for genetic risks

8.2.4 Replicating viral-vector vaccines: risks for dissemination and viral shedding

8.2.5 Inhaled vaccines: immunological rationale and implications for safety, specifically effects on cranial nerves

8.2.6 Intradermal vaccines: immunological rationale and implications for safety, specifically administration errors

8.3 Pharmacovigilance in a Pandemic, Pandemic Preparedness

8.3.1 Challenges for pharmacovigilance in a pandemic situation

8.3.2 Regulatory preparedness of pharmacovigilance in a pandemic

8.3.3 Gap analysis of the pharmacovigilance preparedness checklist

8.3.4 Work-sharing and reliance in accessing safety information about new *medical* products for use in a pandemic

8.3.5 Early detection of safety signals associated with new medications against the infectious pathogens causing the pandemic

8.3.6 Communication: factcheck, tools, psychology; dealing with misinformation (unrealistic fears of infection, hope for miracle cures)

8.4 Medicines for the Prevention and Treatment of HIV, TB, Malaria, Neglected Tropical and Emerging Infectious Diseases (NTDs)

8.4.1 ADRs of antiretroviral medicines used to prevent HIV acquisition and to treat people with HIV

8.4.2 ADRs/AEFI of medicines incl. vaccines used to prevent and treat opportunistic infections in people with HIV (PWH) (TB see 8.4.3)

8.4.3 ADRs/AEFI of medicines incl. vaccines used in prophylaxis and treatment of tuberculosis (TB)

8.4.4 ADRs/AEFI of medicines incl. vaccines used in prophylaxis and treatment of malaria

8.4.5 ADRs/AEFI of medicines incl. vaccines used in prophylaxis and treatment of neglected tropical diseases (NTDs; see WHO list)

8.4.6 ADRs/AEFI of medicines incl. vaccines used in prophylaxis and treatment of emerging infectious diseases (e.g. mpox, Ebola)

Chapter 9: Ineffectiveness of Medicines; Herbals; Food Supplements

9.1 Antibiotic Resistance (AR)

9.1.1 Reasons: inappropriate prescribing and use in humans and livestock, off-label use, patient-related and socio-economic factors

9.1.2 Consequences: hard-to-treat infections, prolonged hospitalisations, nosocomial hospital infections, few new antibiotics and costs

9.1.3 Monitoring, reporting: antibiotic overuse, misuse, off-label use, AR stewardship, electronic health records and AR as reportable ADR

9.1.4 Problem mitigation: education, guidelines; PH initiatives; travel, trade and veterinary livestock regulations and hospital hygiene

9.1.5 The role of PV in encouraging responsible antibiotic use and development of effective low resistance, low allergenic antibiotics

9.2 Ineffectiveness of Other Medicines Including Vaccines

9.2.1 Antiviral resistance; causes/mechanism: incomplete treatment, mutation and selection of surviving viruses, e.g. influenza, hepatitis

9.2.2 Antiretroviral resistance (HIV), including acquired and transmitted and pre-treatment resistance

9.2.3 Antifungal resistance versus *Candida* and *Aspergillus* fungi; causes/mechanism: fungicide overuse in agriculture and medicine; hygiene

9.2.4 Vaccine failure, related to the vaccine: poor quality (SF) impairing prevention of infection, disease and virus transmission

9.2.5 Vaccine failure, related to the patient: patient's insufficient immune response or waning immunity and protection over time

9.2.6 Vaccine-associated enhanced disease: atypical measles, respiratory syncytial virus (RSV) and dengue. Vaccine hypersensitivity (VAH)

Table 1 (continued)

9.3 Risks Associated with Herbs: Phytovigilance

9.3.1 Phytovigilance lens: critical scrutiny of the safety of herbal products, openness to the possibility of risks

9.3.2 Phytovigilance focus: detecting, assessing, preventing specific ADRs of herbs (DILI, AKI); interactions

9.3.3 Phytovigilance core: regulations (AE surveillance, reporting, standardised botanic nomenclature); quality control (GMP, GACP)

9.3.4 Phytovigilance in action: safety cooperation of pharmacists, doctors, industry, regulatory agencies and patients

9.3.5 Phytovigilance academia: herbal education (botany, pharmacy and clinical pharmacology)

9.3.6 Phytovigilance research: scientific investigation into the safety of herbs (required specific knowledge, methods and challenges)

9.4(1-3) Risks Associated with Traditional Medicines (TM)

9.4.1 Traditional medicine: definitions, types and foundations (incl. Ayurveda and Chinese medicine)

9.4.2 ADRs: DILI, AKI, GI toxicity and allergy. Risks of contamination (heavy metals, pesticides and microbes) or adulteration (steroids)

9.4.3 Challenges: advanced analysis and practical applications. Future directions

9.4(4-6) Risks Associated with Food Supplements

9.4.4 Food supplements: definitions, regulatory status and legislation. Types: e.g. vitamins, minerals, amino acids and probiotics

9.4.5 Nutrivigilance in practice: detection and assessment of ADRs, incl. food supplement intake during old age or pregnancy

9.4.6 Food supplement interactions with drugs. Risks owing to addition of drugs to food supplements for doping purposes

Chapter 10: Misuse and Abuse of Medicinal Products**10.1 Types of Substances of Misuse and Abuse; Opioid Antagonists and Their Use**

10.1.1 Definitions: medical use, misuse, abuse, addiction, dependence, substance use disorder (SUD), self-harm and criminal use

10.1.2 Classification of substances of misuse and abuse

10.1.3 Commonly mis- or abused medicines, e.g. opioids (fentanyl), stimulants (MDMA, GHB) and tranquillizers. Emerging trends (cannabis)

10.1.4 Mechanism of action of substances of abuse

10.1.5 Overview and clinical application of medicines against substance use disorder, e.g. opioid antagonists

10.1.6 Withdrawal syndromes: setting and causes, symptoms and treatment

10.2 Substance Use Disorders (SUD)

10.2.1 Epidemiology and risk factors

10.2.2 Neurobiology of addiction and dependence

10.2.3 Social and economic consequences

10.2.4 Clinical management

10.2.5 Prevention strategies and public health interventions

10.3 Self-Harm and Suicide Involving Medicinal Products

10.3.1 Epidemiology and risk factors

10.3.2 Psychology of self-harming and suicidal ideation

10.3.3 Commonly involved substances

10.3.4 Clinical management

10.3.5 Prevention strategies and public health interventions

10.4 Risk Monitoring and Public Health Activities

10.4.1 Data collection: data sources, methods, parameters and limitations

10.4.2 Emerging trends of abuse and misuse, including use for criminal purposes

10.4.3 Public health considerations

10.4.4 Strategies for enhanced risk monitoring

10.4.5 Policy and regulatory responses

Table 1 (continued)

Chapter 11: Medical Device Safety; Radiopharmaceuticals
Sections 11.1–11.3: Medical Device Safety
11.1 Definitions and Risks of Medical Devices

11.1.1 What are medical devices? How do they differ from medicinal products? How are their risks classified?

11.1.2 Drug-device combinations . Examples: drug-eluting stents, inhalers, pre-filled syringes. Regulation according to primary mode of action

11.1.3 DDC risks: material incompatibility, altered drug delivery, drug degradation by device sterilisation, = and others

11.1.4 Software as Medical Device (SaMD). Risks: e.g. decision manipulation, cybersecurity attacks and data inaccuracies (patient mix-up)

11.1.5 In vitro Diagnostic Devices (IVD). Examples: reagents, kits, instruments to diagnose diseases or identify infections (PCR test)

11.1.6 IVD risks: false positives or negative results causing missed diagnoses or wrong treatment. Classes A–D. (e.g. blood group is D)

11.2 Medical Device Regulations Including Development and Investigation

11.2.1 How medical devices are regulated by health authorities around the world

11.2.2 Conduct of clinical investigations involving devices

11.2.3 Human factors engineering (HFE) and usability studies resulting in a Usability Engineering File (UEF)

11.2.4 Manufacturer's responsibility in ensuring performance and safety of devices

11.2.5 Safety responsibilities of notified bodies, authorised agents and other economic operators

11.3 Complaint Handling

11.3.1 Device AEs, product complaints, and their evaluation

11.3.2 Complaint collection and regulatory reporting

11.3.3 Post-marketing surveillance and device complaint trending and analysis

11.3.4 Device risk management: ISO 14971

11.3.5 Device recalls and other market actions

11.4 Risks from Radiopharmaceuticals

11.4.1 Radiopharmaceuticals—an overview

11.4.2 Regulatory framework, focus on risks. Dual regulatory oversight: regulation for pharmaceuticals and for radioactive materials

11.4.3 Guidance by the International Atomic Energy Agency, the International Commission on Radiological Protection and e.g. the EANM

11.4.4 Safety profile of radiopharmaceuticals

11.4.5 Risk management of AEs/ADRs of radiopharmaceuticals

11.4.6 Risk minimisation interventions for ADRs associated with radiopharmaceuticals

Chapter 12: Medication Errors (MEs), Substandard and Falsified Medical Products (SFMPs)
Sections 1–3: Medication Errors: Detection, Assessment, Prevention and Patient Involvement

12.1 Medication Errors (MEs) and Near Misses: Definition, Impact, Place in Health Environment and Reporting

12.1.1 Definition and typology of MEs with and without ADRs, near misses; focus on failing safety measures, persons and equipment

12.1.2 Relationship between ADRs and MEs. ADR—ME integration in pharmacovigilance systems

12.1.3 National ME reporting schemes for professionals and patients

12.1.4 ME burden for public health and economy; global and regional epidemiology; legal, ethical and confidentiality aspects

12.1.5 Reporting of MEs: specific requirements, forms and databases

12.1.6 Institute of Medicine (IOM) report 'To err Is human' and Institute for Safe Medication Practices (ISMP) 'No-blame' approach

12.2 Medication Errors and Near Misses: Detection and Assessment

12.2.1 Active search in specific healthcare settings for MEs by HCPs and patients. Detection of overt or occult MEs in ICSRs

12.2.2 Being aware of risk aspects of clinical procedures and the specific patient susceptibility in high-risk medications prone to MEs

12.2.3 Using SmPCs and professional guidelines as standard of correct medication and for assessment of any non-adherence (i.e. ME)

12.2.4 Assessing the contribution of an ME to the severity or likelihood of an ADR that occurred

Table 1 (continued)

12.2.5 Root Cause Analysis (RCA): Failure Mode and Effects Analysis (FMEA), Human Factors Analysis and Classification System (HFACS)
12.2.6 Assessing the extent of faultiness and options for future preventive measures (persons, medicines, equipment and instructions)
12.3 Medication Error Prevention: Awareness, Technology and Organisation and Patient Involvement
12.3.1 Raising awareness among professionals and patients that MEs can cause ADRs; encouraging reporting of and learning from MEs
12.3.2 Protecting children, elderly, pregnant women; being alert to high-risk drugs and situations such as polypharmacy and transition of care
12.3.3 Using Computerised Physician Order Entry (CPOE) systems, Barcode Medication Administration systems, ML, other AI tools
12.3.4 Preventing MEs through local organisational measures: safe prescription, dispensing and administration
12.3.5 Informing, educating and involving patients in human-centred design of medicines to improve and ensure medication safety
12.3.6 Evaluating the impact of preventive measures: safety dashboards, audits and learning loops; improving/monitoring system resilience
12.4 Substandard and Falsified Medical Products (SFMPs)
12.4.1 Most frequently produced and used drugs that are substandard or falsified (SF)
12.4.2 Clinical consequences and public health impact
12.4.3 Technologies for the detection of SF medical products and prevention strategies
12.4.4 Regulatory framework and global surveillance systems
12.4.5 Strengthening national systems and multi-sectorial collaboration
Chapter 13: Individual Case Safety Reports (ICSRs). (For ICSR reporting systems see Chapter 16)
13.1 Definition, Types, Sources, Contents, Management and Importance
13.1.1 Definition of ICSR, scope, place and significance in official regulations. History: from the Yellow Card to electronic ICSRs
13.1.2 ICSR classification by subject matter: AE/ADR, medication error, quality defect and usage (abuse/misuse)
13.1.3 Key components 1: demographic patient data (initials, age, sex and pregnancy); reporter data (name, profession and workplace)
13.1.4 Key components 2: AE/AEFI (type, severity, dates of occurrence/detection, outcome, dechallenge and rechallenge)
13.1.5 Key components 3: suspect drug (type, dosage, route of administration, start and stop dates)
13.1.6 Key components 4: indication and other patient risk factors (comorbidity, comedication, history, habitus and habits such as alcohol)
13.2 AE/ADR Detection and ICSR Creation and Documentation: Persons and Legal Entities; Forms and Formats
13.2.1 HCPs: their knowledge, diagnostic capability, motivation, professional obligation and barriers to ADR detection and reporting
13.2.2 Patients and caregivers: concerns, expectations, unique observations and their evolving role in patient-centred pharmacovigilance
13.2.3 MAHs and clinical monitors and sponsors of studies: their information sources (medical representatives, studies) and obligations
13.2.4 Regulatory authorities: their role in collecting, analysing, using ICSRs for making PH decisions and giving advice
13.2.5 Public health agencies and health departments: their special role in relation to vaccines safety monitoring and AEFI collection
13.2.6 Standard forms provided by regulators or companies: paper-based or digital (facilitating submission, e.g. ICH E2B)
13.3 Sources of AEs/ADRs, Settings of their Detection and ICSR Creation; Strengths, Limitations (AE/ADR reports from studies: Chapters 15 and 20)
13.3.1 Spontaneous reporting: strengths and limitations versus solicited reports
13.3.2 ICSRs in surveillance programmes: registries, active monitoring, Post-Authorisation Safety Studies (PASS)
13.3.3 Cases from literature: identification, presentation and assessment. Regulatory screening requirements for MAHs
13.3.4 Cases from social digital media including websites, social media programs, Apps and wearables
13.3.5 ICSRs from clinical trials for the development of medicines (study number, name, sponsor and study details) (see also Chapter 15)
13.3.6 Other specifics: medical devices (device and failure details); radiopharmaceuticals; medication errors
13.4 Case Assessment: Quality, Certainty of the Diagnosis, Seriousness and Expectedness (For causality assessment see Chapter 14)
13.4.1 Completeness and reliability of reports: all essential fields of the forms to be filled by structured high-quality data
13.4.2 Certainty of diagnosis: criteria verification based on laboratory/imaging data, grading based on criteria; differential diagnosis
13.4.3 Seriousness and severity of AE/ADR: pathophysiological criteria (e.g. ulcer), treatment/outcome criteria (e.g. hospitalisation)
13.4.4 Expectedness: specific type and severity of ADR in SmPC, investigator's brochure (in RCTs) or safety database as reference

Table 1 (continued)

13.4.5 Case narratives and follow-up assessments: best practices guidance to improve case completeness
13.4.6 Challenges in assessment: lacking information, unclear data, confounders and over/underreporting
Chapter 14: Causality Assessment (CA) of Adverse Events in Pharmacovigilance
14.1 Single Case AEs: Objectives and Fundamental Requirements for Causality Assessment (CA)
14.1.1 Causality assessment of single cases of AEs: individual patient care, litigation, reporting and signal detection
14.1.2 AE as subject of CA must be defined: total sole effect or just contribution to AE severity or likelihood of occurrence?
14.1.3 Suspected cause of AE must be defined: one or more drugs? A specific drug as sole cause or contributor(s)? Synergistic factors?
14.1.4 Role of drug as AE cause must be defined: sufficient or necessary, additive or alternative cause? Place in chain of causes?
14.1.5 If an AE has followed an ME, the contribution of the ME to causing, intensifying or facilitating the AE must be investigated
14.1.6 Reporting-problem: CA is retrospective subjective, hence assumed causality a continuous variable, but reporting a yes/no decision
14.2 Causality Criteria and Recommendations for their Use in the Assessment of Individual Cases
14.2.1 CA methods. Introspective: WHO-UMC; algorithms: Naranjo, Liverpool, 'French' and Kramer. Advantages, limitations. CA criteria used
14.2.2 Chronology incl. de- and re-challenge and pharmacological plausibility incl. AE type aspects (A or B). But not always applicable
14.2.3 Previous case reports. Use only if independent to avoid 'amplification' by carrying over each case as CA argument for the next
(14.2.4 If, in poly-medication, an AE seems to be more severe than the expected sum of individual ADRs: consider drug-drug interaction
14.2.5 Use terms for description of assumed probability of causal relation ('possible' etc.) depending on the quality of documentation
14.2.6 If AE symptom or diagnosis unclear owing to poor report quality/missing criteria: grade analytic/ diagnostic certainty explicitly
14.3 Causality Assessment of Specific Cases; Challenges
14.3.1 AEFI: vaccine product-related reaction; other reasons such as quality defect or medication error
14.3.2 AEs related to herbal or traditional medicines: limited options for causality attribution due to poorly defined pharmacology
14.3.3 Pregnancy outcomes, teratogenicity: confounding due to multiple potential non-drug effectors
14.3.4 Treatment failure and non-response (e.g. vaccines, OCs): severe underlying disease or ME as possible alternative causes
14.3.5 Incident with drug-device combination: defect medical device or contamination as possible cause, not the drug itself
14.3.6 Special setting/situation: AE not caused by drug but by psychological effect, e.g. immunisation stress-related response (ISRR)
14.4 ADR as Capability of a Drug to Cause Harm: Causality Assessment and Impact on Public Health
14.4.1 Detecting new ADRs from case series by assessing and weighting individual causalities, number of cases and consistency among them
14.4.2 Detecting new ADRs, DDIs, syndromes from AE disproportionality in case series; applying directed acyclic graphs (see Chapter 19)
14.4.3 Estimating prior probability and calculating posterior probability in causality assessment: Bayes approach in case series
14.4.4 Combining molecular drug class arguments with ICSRs and studies; applying Hill's criteria for CA (see Chapters 15 and 20)
14.4.5 Using causality arguments when granting authorisation for medicines and as a prerequisite for formulating product information
14.4.6 Assessing public health impact by summing up ADR harm in all cases. Avoiding faults by disregarding individual case causalities
Chapter 15: Pharmacovigilance in Clinical Trials
15.1 Safety Management in Clinical Trials (CTs)
15.1.1 Objectives of PV in CTs: early risk detection, defining risk-relevant information (SmPC, PIL) for marketing authorisation
15.1.2 Documents: study protocol, investigator's brochure, reference safety information (RSI) and informed consent and case report form
15.1.3 Definition of serious adverse event (SAE), serious adverse reaction (SAR), suspected unexpected serious adverse reaction (SUSAR)
15.1.4 Safety data collection: solicited reports about clinical events, open and closed questionnaires. Laboratory data. Checklists
15.1.5 Safety assessment and decision-making: considering new facts, pausing, stopping and adjusting trials
15.1.6 Causality assessment in clinical trials. Key aspects for unblinding. (For causality assessment of single cases see also Chapter 14)
15.2 Regulatory Framework
15.2.1 Relevant guidelines of the International Council for Harmonisation (ICH E2A, E2D, E2F), others (e.g. EU CTR, FDA 21 CFR 312.32)
15.2.2 Registration of clinical trials, databases, key data, numbers: Universal Trial Number, EudraCT Number, NCT Number, ISRCTN
15.2.3 Regulatory requirements and timelines for reporting of SAEs, SUSARs and non-serious AEs

Table 1 (continued)

15.2.4 Regulatory trends, e.g. Clinical Trials Information System (CTIS) and other electronic reporting systems
15.2.5 Safety update reports (PSURs, PBRERs, DSURs): purpose, structure and submission
15.2.6 Documentation and inspection readiness
15.3 Roles of Sponsor, Investigator, and Clinical Monitor in Collecting and Assessing Hazard Data. Safety and Ethical Oversight
15.3.1 The roles of the investigator, sponsor and clinical monitor
15.3.2 The data and safety monitoring plan (DSMP)
15.3.3 Documentation and data quality validation, including coding and de-duplication
15.3.4 Reporting of drug-related problems and compliance with the clinical trial protocol
15.3.5 Hazard identification and preliminary analysis, ongoing detection of emerging safety issues and risk assessment
15.3.6 Data Safety Monitoring Board (DSMB) and ethics committee independent oversight. Ethical and legal considerations
15.4 Risk Assessment and Minimisation in Clinical Trials
15.4.1 Risk assessment in clinical research; regulatory frameworks (e.g. ICH-E2E, EU GVP)
15.4.2 Pre-trial risk identification, anticipated safety concerns, risk minimisation strategies embedded in the clinical trial design
15.4.3 How risk assessment informs the RSI and the development of key documents: SmPC, PIL; VIS for vaccines in the US
15.4.4 Risk communication in the pre-marketing phase
15.4.5 Consequences for regulatory approval decisions and post-approval requirements
Chapter 16: ICSR-Reporting, -Storing and -Analysing
16.1 Common ICSRs Collection Systems (see also Chapter 13)
16.1.1 Reporter: health care professional (HCP), patient/consumer and company. Studies: sponsor
16.1.2 Local, regional or national pharmacovigilance centres
16.1.3 Technical facilitating of suspected AE submission by various Apps, e.g. AUDA-NEPAD Med Safety App developed by WHO and others
16.1.4 Case processing: quality check, anonymisation, clinical and laboratory data and narratives
16.1.5 Correspondence between reporters and recipients: confirmation of receipt, requests for additional data
16.1.6 Coding of AEs/ADRs using MedDRA, patient disease using ICD, medicinal product using WHO DrugGlobal, Rx-Norm, UNICOM
16.2 Special Situations: Cases from Clinical Trials, Medication Errors and Medical Devices
16.2.1 Vaccine AEFI: standard reporting forms provided by national and international organisations, e.g. WHO
16.2.2 MEs incl. near misses: standardised reporting forms. Submission to regulatory bodies (e.g. US: ISMP MERP)
16.2.3 Medical devices: specific reporting forms (e.g. US: FDA 3500A used for device reporting; EU: Manufacturer Incident Report (MIR))
16.2.4 Clinical trials: detection and documentation of AEs and serious adverse events (SAEs) on case report form (CRF) by investigator
16.2.5 Investigator submits CRF to sponsor, who assesses causality and expectedness (SUSAR?), and reports to regulator (and DSMB, EC)
16.3 ICSR Databases
16.3.1 Digitising all data, particularly into the E2B format
16.3.2 Technical means for ICSR submission: overview of ICH guidelines, electronic submission systems
16.3.3 ICSR databases: structure, management systems and quality control. Detecting, merging and eliminating duplicates
16.3.4 Retrieving data from databases, using appropriate search strategies
16.3.5 Important general databases, e.g. VigiBase, EudraVigilance and FAERS. Database diversity: public versus MAH databases
16.3.6 Specific databases, e.g. MAUDE and EUDAMED for medical devices, MEDMARX for MEs, TGA AEFI for vaccines
16.4 ICSR Series Documentation and Analysis (For disproportionality analysis and signal detection see Chapter 19)
16.4.1 Line listings, summary tabulations and other formats
16.4.2 Dashboards
16.4.3 Descriptive non-statistical analyses of case series
16.4.4 Limitations of ICSRs data analysis
16.4.5 Open and graded access

Table 1 (continued)

Chapter 17: Real-World Data (RWD) and Real-World Evidence (RWE) for Pharmacovigilance Purposes

17.1 Paper-Based Health Records: Foundations and Limitations

17.1.1 Persistence of paper records in routine care

17.1.2 Fragmentation across care settings

17.1.3 Manual effort and transcription challenges

17.1.4 Risks of loss, error and inconsistency

17.1.5 Local practices and contextual insights

17.2 Electronic Health Records (EHRs) and Digital Health

17.2.1 Standardisation and interoperability

17.2.2 Seamless provider-to-provider communication

17.2.3 E-prescriptions and clinical notes

17.2.4 Patient-facing tools and wearables

17.2.5 Barriers to adoption and equality in access

17.3 Monitoring and Surveillance: from Local to Global Safety

17.3.1 Early signal detection and risk identification

17.3.2 Real-time monitoring of interventions

17.3.3 Local surveillance complementing central networks

17.3.4 Rare adverse events and special populations

17.3.5 Emergency preparedness and rapid response

17.3.6 Patient-reported outcomes as added value

17.4 Data Analysis with Privacy by Design: Platforms and Networks

17.4.1 Large-scale, secure analytical platforms

17.4.2 Federated models for local data protection

17.4.3 Multi-database and cross-country collaboration

17.4.4 Governance and transparency frameworks

17.4.5 Harmonisation, data quality and sustainability

Chapter 18: Artificial Intelligence (AI) in Pharmacovigilance

18.1 Foundations of Artificial Intelligence for Pharmacovigilance

18.1.1 Defining AI: core concepts and relevance

18.1.2 Essential AI terminology for PV professionals

18.1.3 Machine Learning paradigms: supervised and unsupervised approaches

18.1.4 Basics of Deep Learning

18.1.5 AI development pipelines: from data to deployment in pharmacovigilance

18.1.6 Case studies: real-world applications of AI in pharmacovigilance

18.2 Language Models in Pharmacovigilance

18.2.1 Natural Language Processing (NLP): principles and techniques for analysing safety data

18.2.2 Language models in pharmacovigilance: capabilities, risks and practical limitations

18.2.3 Small and Large Language Models (LLM): concepts, architectures and differences

18.2.4 Prompt engineering: basics and advanced principles

18.2.5 Outputs of language models: accuracy and reliability

18.3 AI Applications in Pharmacovigilance

18.3.1 Safety data recognition and extraction

18.3.2 AI-assisted coding of adverse reactions

18.3.3 Ensuring data quality and completeness

Table 1 (continued)

18.3.4 Leveraging AI for causality assessment
18.3.5 Using AI for supporting signal management
18.3.6 Using agentic AI for supporting and completing PV tasks
18.4 Ethics, Trustworthiness, and Ecological Impact
18.4.1 Ethical principles for AI in pharmacovigilance
18.4.2 Transparency, explainability, and accountability in AI-enabled PV systems
18.4.3 Data governance and privacy protection in safety-related AI applications
18.4.4 Building trust: validation, robustness and risk management for AI in pharmacovigilance
18.4.5 Ethical use of generative AI
18.4.6 Environmental and ecological impact of AI
Chapter 19: Signal Detection and Management
19.1 Introduction to Signal Detection
19.1.1 Key definitions of a signal, its historical perspectives, importance and objectives
19.1.2 Index cases: identification, assessment and importance
19.1.3 Signals of disproportionate reporting: frequentists methods (e.g. PRR, ROR); Bayesian methods
19.1.4 Bias and confounding factors
19.1.5 Stakeholders in the signal detection and management process
19.2 Assessment and Interpretation of Safety Signals
19.2.1 Signal detection from ADR case series by non-statistical medical overview and judgement
19.2.2 Signals of disproportionate reporting: screening and selection
19.2.3 Signal validation and prioritisation
19.2.4 Signal assessment, substantiation and evidence weighting
19.2.5 Risk assessment and developing recommendations for action
19.2.6 Publishing disproportionality analyses: the READUS-PV guidelines
19.3 Challenges in Signal Detection and Management
19.3.1 The role of AI
19.3.2 Social media data
19.3.3 Real-World Evidence integration
19.3.4 Patient involvement
19.3.5 Transparency and standardization
19.4 Special Situations
19.4.1 Vaccines
19.4.2 Drug interactions
19.4.3 Identifying drug-induced syndromes
19.4.4 Signals in resource-limited settings: approaches and challenges
19.4.5 Signals in specific populations
Chapter 20: Real-World Data for Post-Marketing Surveillance; Pharmacoepidemiology
20.1 Definitions, Objectives and Basic Concepts
20.1.1 Key definitions: absolute and relative risk measures
20.1.2 Real-world data sources
20.1.3 Selection of appropriate reference groups
20.1.4 Observed/expected analyses
20.1.5 Post-Authorisation Safety Studies (PASS): definition, rationale and objectives
20.1.6 Feasibility assessment for observational studies; use of AI
20.2 Observational Study Designs: Types, Strengths and Limitations

Table 1 (continued)

20.2.1 Cohort studies; characteristics, strengths and limitations

20.2.2 Case-control studies (CCS), incl. nested case-control studies and case-non-case studies: strengths and limitations

20.2.3 Case-crossover and self-controlled case series

20.2.4 Target trial emulation

20.2.5 Cohort event monitoring and other observational designs

20.2.6 Cross-sectional studies

20.3 Bias, Confounding and Advanced Analytical Methods

20.3.1 Definitions of bias and confounding

20.3.2 Major biases and mitigation strategies

20.3.3 Sensitivity and quantitative bias analysis (QBA)

20.3.4 Major types of confounding and confounding control strategies; propensity score (PS) methods

20.3.5 Time dependent versus time fixed approach

20.3.6 Advanced causal inference methods

20.4 Multi-Database Real-World Data Studies

20.4.1 Definitions, evolution and rationale

20.4.2 Data harmonisation and common data models

20.4.3 Federated versus centralised architectures

20.4.4 Strengths and limitations of multi-database studies

20.4.5 Approaches and networks; use of AI

Chapter 21: Benefit-Risk (B-R) Assessment

21.1 Benefit as Degree and Probability of Mitigation or Prevention of a Specific Disease by a Specific Medicinal Product

21.1.1 Dual meaning of benefit: (a) cause or possibility of something good in the past or present, (b) probability of it in the future

21.1.2 Benefit as reduction of severity or frequency of disease parameters or disease occurrence resp. (the latter e.g. by vaccines)

21.1.3 Disease parameters: pathophysiological and clinical events (e.g. urticaria, ulcer and pain), surrogate markers incl. biomarkers

21.1.4 Disease parameters: treatment and occurrences to the patient's situation (e.g. defibrillation, hospitalisation, death, costs)

21.1.5 Disease seriousness as extent of instantaneous deviation of parameters from norm and duration, or threat to the patient

21.1.6 Learning from health insurances: weighting of disease seriousness, likelihood, impact and their mitigation (drug-related benefit)

21.2 ADR-Related Harm and Risk as Composed of Seriousness and Frequency of All Relevant ADRs of a Medicinal Product

21.2.1 Types of drug-related harm: ADRs like disease parameters (see 21.1.3, 21.1.4: pathophysiological, clinical or situation effects)

21.2.2 ADR-related harm composed of instantaneous suffering and duration. Risk as future probability of harm

21.2.3 Further types of drug-related problems (DRPs): DDIs, misuse, likely MEs, ineffectiveness, psychological stress reactions and PROs

21.2.4 Risk as extent of harm times frequency of manifestation. Further factors: causal relation, statistical significance and reversibility

21.2.5 Quantifying and weighting risk: severity/seriousness scales, QALYs; hazard ratios, incidence rates, NNH and risk differences

21.2.6 Adding up all risks from all ADRs associated with a particular medicinal product to determine the total risk

21.3 Balancing Benefit versus Risk, Comparing B-R across Different Treatments and Taking into Account Uncertainties

21.3.1 Taking into account patient and population heterogeneity: variable disease severity, natural course and risk of occurrence

21.3.2 Patient and population heterogeneity: age, sex, genetics, comorbidities, social determinants of drug response and tolerability

21.3.3 Considering data source reliability, uncertainties owing to bias and confounding. Estimating the evidence level

21.3.4 Assessing net benefit by comparing the risk of untreated disease with the risk of treated disease plus that of all ADRs (INHB)

21.3.5 Comparing B-R across treatment options; estimating the added value of a new drug; criteria for calculating ratios or differences

21.3.6 Performing sensitivity analyses: best case/worst case scenarios

21.4 Integration Models and Frameworks

21.4.1 Necessary and available data and tools for structured B-R estimation: meta-analyses, simulation models (e.g. Markov, PSM)

21.4.2 Integration of patient- and stakeholder perspectives in B-R assessment and decision-making

21.4.3 Integration models: BRAT, ProACT-URL, graphical visualisation, FDA grid, Multi Criteria Decision Analysis and Bayesian models

21.4.4 Scenarios of B-R assessment: marketing authorisation of new drugs, PV of marketed ('old') drugs

21.4.5 Scenarios of B-R assessment: individual cases and public health—both, retro- and prospective aspects

Table 1 (continued)

21.4.6 Regulatory flexibility in face of uncertainties, e.g. suspension of marketing authorisation pending PASS, conditional approval
Chapter 22: Risk Minimisation Approaches to Ensure that the Benefit Exceeds the Risks of the Medicine
22.1 Principles, Development and Implementation of Risk Minimisation Interventions
22.1.1 Definition, objectives, scope of risk minimisation as part of risk management planning
22.1.2 Designing risk minimisation measures (RMM) likely effective to achieve set objectives within clinical contexts
22.1.3 Implementing risk minimisation interventions and communication
22.1.4 Addressing ethical, cultural and operational challenges when requiring and implementing risk minimisation interventions
22.1.5 Integration of accumulating data into benefit-risk assessment throughout the product life-cycle for decisions on risk minimisation
22.2 Routine Risk Minimisation Interventions
22.2.1 Packaging, labelling, product information for patients, care givers and healthcare professionals and digital tools
22.2.2 Prescribing and dispensing requirements; safe use advice
22.2.3 Oversight of routine risk minimisation by the regulatory authority
22.2.4 Impact of single case and aggregated pharmacovigilance data on routine risk minimisation strengthening
22.2.5 Overcoming barriers affecting the effective implementation of routine risk minimisation
22.3 Additional Risk Minimisation Interventions
22.3.1 Definition, criteria, and regulatory context of additional risk minimisation measures (aRMMs); digital tools
22.3.2 Educational aRMM for patients and healthcare professionals
22.3.3 aRMM programmes for risk minimisation control, controlled access and controlled/restricted distribution or pregnancy prevention
22.3.4 Real-time feed-back for adaptive and dynamic aRMMs
22.3.5 Overcoming barriers affecting the effective implementation of aRMMs
22.4 Assessing the Effectiveness of Risk Minimisation Interventions
22.4.1 Principles, methods, and frameworks of risk minimisation effectiveness evaluation; planning cycles for iterative feedback
22.4.2 Assessing the dissemination process and further logistical implementation tools and metrics, including digital tools
22.4.3 Assessing knowledge, attitude, behavioural outcomes, impact and unintended outcomes
22.4.4 Quantitative and qualitative study designs for effectiveness evaluation
22.4.5 Challenges faced in risk minimisation effectiveness evaluation
Chapter 23: PV Systems at Industry and Competent Authorities, Quality Management; Audits, Inspections
23.1 Pharmacovigilance Systems: Settings, Persons, Processes and Preparedness
23.1.1 Settings: regulatory bodies, industry, regional centres/hospitals; organisation, resources, infrastructure and legal context
23.1.2 Qualified Person for Pharmacovigilance (QPPV) and further personnel: recruitment, job descriptions, qualifications, continuous training
23.1.3 Processes: establishing, maintaining and applying tools, computerised systems, workflows, procedures and transparency
23.1.4 Record retention policies, record management processes; assurance of data security and integrity; personal data protection
23.1.5 Preparedness plans and back-up system for business continuity, urgency, public health emergency; crisis management plans
23.2 Specifics for Industry Pharmacovigilance Systems
23.2.1 Collecting, archiving, transmitting information; assessing ICSRs, signals, studies, literature and PSURs/PBRERs
23.2.2 Organisation for local and global operations; contractual arrangements with partner companies and sub-contractors
23.2.3 External interactions, role and responsibilities in jurisdictions
23.2.4 Pharmacovigilance system master file (PSMF): content, access, updates, role for quality management and inspections
23.2.5 Electronic tools incl. databases; digital tools; AI tools
23.3 Quality Management Systems
23.3.1 Concepts of quality: quality principles, quality objectives, quality requirements, quality system and quality cycle
23.3.2 Documentation: organigram, quality plan, quality manual (work instructions, SOPs), quality records, training plans and records
23.3.3 Processes: quality and compliance management; performance planning and indicators, monitoring, evaluation and reporting
23.3.4 Specific processes for adhering to scientific standards: selecting experts, avoiding conflicts of interests and mitigating biases
23.3.5 Continuous quality improvement: capacity-building, sustainability and system resilience; future-proofing and advancements
23.3.6 Audit planning and follow-up for quality improvement; inspection-readiness
23.4 Pharmacovigilance Audits and Inspections

Table 1 (continued)

23.4.1 Types of audits/inspections: routine or for-cause, announced or unannounced; partnered and subcontracted activities
23.4.2 Subject of audit/inspection: quality manual, product labelling; collection and processing sites, reporting units
23.4.3 Scrutiny: technical equipment, database validation, correct ICSR and PSUR handling, medical assessment and staff qualification
23.4.4 Handling of typical failures: delayed ICSR or PSUR reporting, no follow-up, database issues, inadequate SOPs and non-compliance
23.4.5 Post-inspection: informing the company about observations, grading of findings; writing an inspection report with documentation
23.4.6 CAPA management, regulatory risk-mitigation, company actions follow-up, non-compliance warning, enforcement, information sharing
Chapter 24: Smart PV, PV in All Continents, International Organisations and Public Health Programmes
24.1 Smart Pharmacovigilance: PV as Part of Regulatory System Strengthening
24.1.1 Principles of smart PV: optimal use of human and material resources, local relevance, high performance according to indicators
24.1.2 Developing a PV system using the WHO Global Benchmarking Tool (GBT): resources structure, tools, processes, stakeholders
24.1.3 Prioritisation of PV according to country's product pipeline, updating AE reporting strategies for risk detection and management
24.1.4 Reliance, information exchange, collaboration of interested parties as mechanisms to enhance system efficiency and effectiveness
24.1.5 Facilitating compliance with PV regulatory requirements by MAHs, importers, distributors and manufacturers in local environments
24.1.6 Competency-based capacity building to equip stakeholders with the appropriate level of skills for effective PV implementation
24.2 Pharmacovigilance in Regional and Global Public Health (PH) Settings
24.2.1 Elements of Public Health Programmes (PHP); role of WHO; regional and global projects and funding (e.g. BMGF, GFATM)
24.2.2 PV in major PH programmes on communicable (HIV, TB, malaria and neglected tropical diseases) or non-communicable diseases
24.2.3 PV in specific/local PH programmes, e.g. antimicrobial mass administration, immunisation and pregnancy/maternal/newborn care
24.2.4 PH data collection and PV tools, e.g. CEM, TSR, surveys; advantages/disadvantages versus SRS; PV methods for signals relevant to PH
24.2.5 PV in PH emergency programmes, e.g. pandemics; PV in crisis management, e.g. medicines quality defects and ineffectiveness
24.2.6 Collaboration in PV: public health incl. regulatory organisations; coordination of PV across PH programmes and clinical settings
24.3 Pharmacovigilance in All Continents
24.3.1 PV in Europe (EMA, others)
24.3.2 PV in the Middle East and North Africa
24.3.3 PV in Asia
24.3.4 PV in Africa
24.3.5 PV in the Western Pacific
24.3.6 PV in the Americas (USA, others)
24.4 Cooperative International Organisations
24.4.1 WHO; WHO Collaborating Centres Uppsala and Rabat; WHO advisory committees ACSoMP, GACVS; regional organisations/initiatives
24.4.2 Council for International Organizations of Medical Sciences (CIOMS); International Organization for Standardization (ISO)
24.4.3 International Council for Harmonisation (ICH): guidelines on clinical safety data management and medical terminology (MedDRA)
24.4.4 International learned societies and other PV training organisations: WHO, UMC, ISoP, ISPE, IUPHAR and Global Medicines Safety Hub
24.4.5 Pharmaceutical industry associations: IFPMA, BIO, IGBA and Global Self-Care Federation
24.4.6 Patient organisations: International Alliance of Patients' Organizations (IAPO) and EURORDIS
Chapter 25: Pharmacovigilance in Clinical Settings; Eco-Pharmacovigilance (Eco-PV); Patient Participation
25.1 Pharmacovigilance in Clinical Settings
25.1.1 Safety culture: enhancing hazard awareness, risk management, and readiness to detect, treat and report medicines-related AEs
25.1.2 Healthcare systems: prioritising and integrating PV for ADR surveillance and prevention in clinical care; hospital PV-centres
25.1.3 PV methods: optimised clinical data collection for contributing to risk identification and assessment according to signal types
25.1.4 Assessing benefit-risk for individuals and communities in given contexts; differences to regulatory assessments
25.1.5 Assessing the burden of medicine-induced diseases on patients, healthcare systems, clinical settings and health expenditure
25.2 Eco-Pharmacovigilance
25.2.1 Introduction to eco-pharmacovigilance and green medicine
25.2.2 Distribution of pharmaceuticals in ecosystems and their impact
25.2.3 Regulatory frameworks and guidelines; risk mitigation policies
25.2.4 Stakeholder engagement and education about eco-PV
25.2.5 Eco-PV systems and reporting of medicines-related problems in this respect
25.3 Patient Information

Table 1 (continued)

25.3.1	Information needs and health literacy regarding the use of medicines
25.3.2	Information on medication errors and the role of patients in medication safety
25.3.3	Strengthening information exchange between patients and HCPs for patient-centered care
25.3.4	Improving medicines labels and leaflets
25.3.5	Encouraging and empowering patients to report AEs for better medication safety
25.3.6	Providing digital tools and technology for enhancing patient information
25.4	Patients in Medicines Development and Regulation
25.4.1	Evolution and value of contributions from patients and patient organisations (WAPS, IAPO) to pharmacovigilance
25.4.2	Frameworks, objectives and methods of patient engagement in regulatory decision-making
25.4.3	Patient engagement in clinical trials and post-authorisation research: capturing experience, preferences and outcomes; PCORnet
25.4.4	Incorporating patient experiences into shared decision-making
25.4.5	Ethical, cybersecurity and confidentiality considerations and challenges for patient engagement
25.4.6	The future of patient engagement in a changing environment, including digitalisation
Chapter 26: Sources of Information about PV; Training Material; Risk Communication	
26.1	General and Specific Literature; Databases and Search Engines; Journals and Bulletins; Use of AI
26.1.1	Overview of pharmacovigilance literature sources
26.1.2	Key pharmacovigilance databases and search engines
26.1.3	Notable journals and bulletins in pharmacovigilance
26.1.4	Literature monitoring in pharmacovigilance: regulatory requirements
26.1.5	Applications of Artificial Intelligence in pharmacovigilance literature monitoring
26.2	Materials and Training Courses: Worldwide, Regional and Context-Specific
26.2.1	Core education and training materials e.g. textbooks, guidelines, manuals and online courses/eLearning
26.2.2	Other relevant materials e.g. resource repositories/libraries, templates, handbooks, factsheets, video/webinar series and podcasts
26.2.3	Specific training needs by role/sector (HCPs, industry, regulators etc.) and product type (e.g. antibiotics, vaccines and devices)
26.2.4	International providers of training and qualifications, e.g. WHO, UMC, ISoP, Eu2P, Am2P, DSRU, DIA, RCC, TGHN, key universities
26.2.5	Regional, national or locally relevant training from health authorities, public health programmes, regional organisations, etc.
26.2.6	Hands-on practical training
26.3–26.4	Risk Communication
26.3	Risk Communication Process
26.3.1	Patient-centred care and public health: benefit versus risk-dialogue; shared therapeutic decisions; safety management
26.3.2	Medicines use: communication on social-ecological levels; clinical, cultural, economic and political contexts; public discourse
26.3.3	Risk psychology and governance: behaviour change models and tools; developing and implementing tailored communication strategies
26.3.4	Ethical, legal, regulatory and public health frameworks: guidance documents; communication planning tools
26.3.5	Communication management in public health emergencies: providing helpful alerts and advice, dealing with mis- and disinformation
26.3.6	Communication monitoring: formative and evaluative research with patient and healthcare engagement
26.4	Risk Communication Stakeholders
26.4.1	Mapping local and global stakeholders and community leaders, their roles and relationships; fostering collaboration
26.4.2	General, scientific and social media landscape; information seeking behaviours; interaction and presentation in media
26.4.3	Communicating with industry, regulators/policy makers and healthcare groups according to legal mandates, rules and oversight
26.4.4	Communicating with patient organisations: tailoring of information (e.g. PILs), tools and channels according to health literacy
26.4.5	Communicating with healthcare professionals: tailoring contents (e.g. product information), tools, channels, and workflows
26.4.6	Communication transparency: tailored access to ICSR databases, study registries, regulatory documents and stakeholder events

ACE angiotensin converting enzyme, *ACSoMP* (WHO) Advisory Committee on Safety of Medicinal Products, *ADC* antibody-drug conjugate, *ADR* adverse drug reaction, *AE* adverse event, *AEFI* adverse event following immunisation, *AESI* vaccine product-related events of special interest, *AGEP* acute generalised exanthematous pustulosis, *AI* artificial intelligence, *AKI* acute kidney injury, *ALT* alanine transaminase, *AR* antibiotic resistance, *ARB* angiotensin II receptor blocker, *aRMM* additional risk minimisation measure, *AST* aspartate aminotransferase, *ATC* Anatomical Therapeutic Chemical classification system, *AUDA-NEPAD* African Union Development Agency-New Partnership for Africa's Development, *BIO* Biotechnology Innovation Organization, *BMGF* Bill and Melinda Gates Foundation, *BPH* benign prostatic hyperplasia, *B-R* benefit-risk, *BRAT* Benefit-Risk Assessment Team, *CA* causality assessment, *CAPA* corrective and preventive action, *CAR-T* chimeric antigen receptor T cell, *CCB* calcium channel blocker, *CCS* case-control study, *CDM* Common Data Model, *CEM* cohort event monitoring, *CEPI* Coalition of Epidemic Preparedness Innovations, *CFR* code of federal regulations, *CIOMS* Council of International Organizations for Medical Sciences, *CNS* central nervous system, *COX-2* cyclooxygenase-2, *CPOE* computerised physician order entry, *CRF* case report form, *CT* clinical trial, *CTIS* Clinical Trials Information System, *CTR* clinical trial regulation, *CYP* cytochrome P450, *DDC* drug-device combination product, *DDI* drug-drug interaction,

Table 1 (continued)

DIA Drug Information Association, *DIC* disseminated intravascular coagulation, *DILI* drug-induced liver injury, *DoTS* dose, time course, relevant susceptibility, *DRESS* drug reaction with eosinophilia and systemic symptoms, *DRP* drug-related problem, *DSMB* data safety monitoring board, *DSMP* drug safety monitoring plan, *DSRU* Drug Safety Research Unit, *DSUR* development safety update report, *EANM* European Association of Nuclear Medicine, *EC* ethics committee, *EHR* electronic health record, *EIDOS* Extrinsic, Intrinsic, Distribution, Outcome, Sequela, *EMA* European Medicines Agency, *ENCePP* European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, *EPAR* European Public Assessment Report, *EU-CTR* EU Clinical Trials Regulation, *EU GVP* EU good pharmacovigilance practices, *EURODIS* rare disease patients in Europe, *EVDAS* EudraVigilance Data Analysis System, *EVMPD* EudraVigilance Medicinal Product Dictionary, *FAERS* FDA Adverse Event Reporting System, *FDA* US Food and Drug Administration, *FMEA* failure mode and effects analysis, *GABA* gamma aminobutyric acid, *GACP* Good Agricultural and Collection Practices, *GACVS* (WHO) Global Advisory Committee on Vaccine Safety, *GBS* Guillain-Barré syndrome, *GBT* Global Benchmarking Tool, *GFATM* Global Fund for AIDS, Tuberculosis and Malaria, *GHB* gamma-hydroxybutyric acid, *GI* gastrointestinal, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *GLP-1RA* (or *GLP1RA*) GLP-1 receptor agonist, *GMP* Good Manufacturing Practices, *GMSH* Global Medicines Safety Hub, *GVP* good vigilance practice, *H2RA* H2-receptor antagonists, *HCP* healthcare professional, *HFACS* Human Factors Analysis and Classification System, *HFSR* hand-foot skin reaction, *HILI* herb-induced liver injury, *HIV* human immunodeficiency virus, *HRT* hormone replacement therapy, *IAEA* International Atomic Energy Agency, *IAPO* International Alliance of Patients' Organizations, *IB* investigator's brochure, *ICANS* immune effector cell-associated neurotoxicity syndrome, *ICD* International Classification of Diseases, *ICH* International Conference on Harmonization, *ICH E2B* guideline no. E2B of the International Conference on Harmonisation, *ICSR* individual case safety report, *IFPMA* International Federation of Pharmaceutical Manufacturers and Associations, *IGBA* International Generic and Biosimilar Medicines Association, *IL* interleukin, *INHB* incremental net health benefit, *ISMP MERP* Institute for Safe Medication Practices National Medication Errors Reporting Program, *ISO* International Organisation for Standardisation, *ISO*P International Society of Pharmacovigilance, *ISPE* International Society for Pharmacoepidemiology, *ISRCTN* The International Standard Randomised Controlled Trial Number, *ISRR* immunisation stress-related response, *IT* information technology, *ITT* intention-to-treat, *IUPHAR* International Union of Basic and Clinical Pharmacology, *IVD* in vitro diagnostic device, *KPI* key performance indicator, *LLM* large language model, *MAB* monoclonal antibody, *MAH* marketing authorisation holder, *MAUDE* manufacturer and user facility device experience, *MCDA* multi-criteria decision analysis, *MDMA* methylenedioxymethylamphetamine, *MDR* Medical Device Regulation, *ME* medication error, *MedDRA* Medical Dictionary for Regulatory Activities, *MEDMARX* Medication Adverse event Reporting and eXploration, *MI* myocardial infarction, *MIR* Manufacturer Incident Report, *ML* machine learning, *NAION* non-arteritic anterior ischemic optic neuropathy, *NCC MERP* National Coordinating Council for Medication Error Reporting, *NCT* National Library of Medicine—Clinical Trial, *NLP* natural language processing, *NNH* number needed to harm, *NNT* number needed to treat, *NOAC* (non-vitamin K antagonist) novel oral anticoagulant, *NSAID* non-steroidal anti-inflammatory drug, *NTD* neglected tropical disease, *OC* oral contraceptive, *OHDSI* Observational Health Data Sciences and Informatics, *OMOP* Observational Medical Outcomes Partnership, *PAER* periodic adverse experience report, *PASS* post-authorisation safety study, *PBRER* periodic benefit risk evaluation report, *PCORnet* Patient-Centered Outcomes Research Network, *PCR* polymerase chain reaction, *PD* pharmacodynamics, *PEM* prescription event monitoring, *PGx* pharmacogenetics or pharmacogenomics, *PH* public health, *PHP* public health programme, *PIDM* WHO Programme for International Drug Monitoring, *PIL* patient information leaflet, *PK* pharmacokinetics, *PML* progressive multifocal leukoencephalopathy, *PPA* per-protocol analysis, *PPI* proton pump inhibitor, *PRO* patient-reported outcome, *PrOACT-URL* Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, Linked decisions, *PROSPER* Patient-Reported Outcome Measures in Safety Event Reporting, *PRR* proportional reporting ratio, *PS* propensity score, *PSM* partitioned survival models, *PSMF* pharmacovigilance system master file, *PSUR* periodic safety update report, *PV* pharmacovigilance, *PWH* people with HIV, *QALY* quality-adjusted life year, *QBA* sensitivity and quantitative bias analysis, *QPPV* qualified person for pharmacovigilance, *RCA* root cause analysis, *RCC* Regulatory Compliance Certification, *RCT* randomised clinical trial, *READUS-PV* Reporting of A Disproportionality analysis for drUG Safety signal detection using spontaneously reported adverse events, *REMS* risk evaluation and mitigation strategy, *RRM* risk minimisation measures, *RMP* risk management plan, *ROR* reporting odds ratio, *RSI* reference safety information, *RSV* respiratory syncytial virus, *RWD* real-world data, *RWE* real world evidence, *SAE* serious adverse event, *SaMD* software as medical device, *SAR* serious adverse reaction, *SCAR* Serious Cutaneous Adverse Reaction, *SFMP* substandard and falsified medical product, *SGLT2i* sodium-glucose co-transporter-2-inhibitor, *SJS* Stevens-Johnson syndrome, *SmPC* summary of product characteristics, *SOP* standard operating procedure, *SRS* spontaneous reporting system, *SSRI* selective serotonin reuptake inhibitor, *STROBE* Strengthening the Reporting of Observational Studies in Epidemiology, *SUD* substance use disorder, *SUSAR* suspected unexpected serious adverse reaction, *TB* tuberculosis, *TCR-T* T-cell receptor T cell, *TdP* torsades de pointes, *TEN* toxic epidermal necrolysis, *TGA* Therapeutic Goods Administration, *TGHN* The Global Health Network, *TIN* acute tubulointerstitial nephritis, *TIS* teratogen information services, *TK* tyrosine kinase, *TLS* tumour lysis syndrome, *TM* traditional medicines, *TNF- α* tumour necrosis factor α , *TSR* targeted spontaneous reporting, *TTS* thrombosis with thrombocytopenia syndrome, *UMC* Uppsala Monitoring Centre, *UNICOM* Up-scaling the global univocal identification of medicines, *VAED* vaccine-associated enhanced disease, *VAH* vaccine-associated hypersensitivity, *VIS* vaccine information statement, *VITT* vaccine-induced immune thrombotic thrombocytopenia, *VTE* venous thromboembolism, *WAPS* World Alliance for Patient Safety, *WHO* World Health Organisation

3 Results

3.1 Chapters, Sections, Subsections

The updated curriculum retained the structure of the original curriculum, organising the field of PV into chapters, with each chapter divided into four sections, and each section further subdivided into five or six subsections. This preserves a symmetrical three-level hierarchical structure. However, the

number of chapters increased from 15 to 26. Certain topics were not broad enough to justify standalone chapters but were sufficiently distinct to establish and fill specific sections of their own and to require dedicated headings. These were incorporated into 13 'combination chapters' with multi-part headings. To maintain consistency and conciseness, the length of each heading was limited to 129 characters, including spaces. As a result, abbreviations were used more frequently, requiring a more extensive list of abbreviations

than in the original curriculum. All chapters, sections, and subsections headings are presented in Table 1. In total, the updated curriculum comprises 696 headings.

3.2 Practical Tasks

The updated curriculum again includes a structured set of practical tasks designed to support the development of applied competencies in PV. In contrast to the theoretical components of chapters 1–10, which primarily address foundational knowledge, practical tasks are introduced from chapter 11 onwards, where applied skills become essential.

The practical tasks were designed according to a competency-oriented approach and generally include: (1) a defined input or scenario, such as individual case safety reports (ICSRs), datasets, guidelines, regulatory domains, case studies or simulated situations; (2) an applied analytical, regulatory or a communication-related activity; and (3) an expected output, such as assessment, regulatory document, risk minimisation proposal, communication materials or study design. The tasks cover a broad range of competency domains, including causality assessment, signal detection, pharmacoepidemiology, regulatory evaluation, quality management, risk management, patient engagement, communication and the use of digital tools and artificial intelligence.

Given the diversity of PV activities, the practical tasks vary in scope and complexity. Some focus on structured technical exercises, e.g. coding ICSR, conducting disproportionality analyses, or appraising observational studies, whereas others emphasise critical judgment, communication, system design, or strategic decision-making in real-world scenarios. Several tasks also require consideration of regional context, resource limitations, public health settings and patient perspectives.

Compared with the original 2014 curriculum, the updated curriculum places greater emphasis on skill-based training, interdisciplinary thinking, digitalisation and real-world application. Consequently, many practical tasks involve the use of electronic databases, AI-supported tools, regulatory guidance documents or real-world datasets. The number and diversity of practical tasks have also increased substantially. Their total number is now 125.

The practical tasks are intended to serve as adaptable educational frameworks that can be modified according to the training objectives and setting. Depending on the audiences, some tasks may well prove too trivial for some participants while being unnecessarily demanding for others. In such cases, the instructor can expand and increase the complexity of a task in the first scenario, whereas in the second, she or he might consider simplifying or even omitting it entirely.

To maintain the conciseness of the printed publication, the practical tasks are provided as Electronic Supplementary Material (Online Resource Annex I).

3.3 References

The experts were asked to suggest literature references for their respective chapters or sections and to classify them into ‘basic’ and ‘specific’ references. Basic references were intended to include comprehensive textbooks, guidelines, reviews and, in exceptional cases, landmark publications such as the classification of ADRs into Type A and Type B reactions by Rawlins and Thompson, or publications introducing fundamentally new concepts. Specific references were intended to highlight publications relevant to individual subsections or topics.

Where appropriate, textbooks and guidelines referenced in the original curriculum were retained with newer editions cited when available. Emphasis was placed on guidelines and recommendations from WHO, CIOMS and ICH.

Given the large number of references proposed by the co-authors, the reference list is provided as Electronic Supplementary Material (Online Resource Annex II), as in the original curriculum. Differentiating between basic and specific references was sometimes challenging and depended on the subjective judgement of the respective experts. References were therefore retained according to their chapter and section assignment. The number of references varies across chapters and sections reflecting differences in scope and the decisions of individual working groups. Several textbooks with broad topic coverage were repeatedly cited in connection with various chapters and sections. In total, the updated curriculum includes 209 basic and 260 specific references. To limit the length of the printed publication, only five references are cited for clarification in the main text.

4 Discussion

4.1 Contents, Scope and Depth of the Curriculum

The updated curriculum provides a comprehensive and structured inventory of PV subject matter in a three-level, hierarchical format: chapters, sections and subsections. It covers an expanded range of scientific, clinical, methodological, regulatory and public health topics. These include genetic testing, advanced therapy such as Chimeric Antigen Receptor T-cell (CAR T-cell) and gene therapy, monoclonal antibodies, glucagon-like peptide-1 receptor agonists, mRNA vaccines, antimicrobial resistance, medical device safety, real-world evidence, AI, risk management planning, public health programmes, EcoPV, patient involvement and risk communication and also addresses frequently occurring and serious ADRs of commonly used, well-established medicines.

A major strength is its broad and multidisciplinary foundation, developed through collaboration among

experts from academia, regulators, industry, NGOs and consultant entrepreneurs across the world regions. In addition, it derives credibility from the joint leadership and expertise of the WHO (including its advisory groups and collaborating centres) and ISoP, reflecting their extensive experience and cooperation in supporting PV capacity-building across countries with diverse healthcare systems, resources and levels of industrialisation.

Although some chapter headings overlap with those of existing PV courses, the curriculum is distinguished by the breadth and granularity of its content, its structured three-level organisation and its integration of both theoretical and competency-oriented practical components as well as its supplementation by a significant number of relevant literature references.

4.2 Using the Curriculum

The structure of the curriculum's updated version makes it possible to focus on specific topics in varying levels of depth, while maintaining the broader context of PV. The flexibility is supported by three main features:

First, the large number of theoretical modules, arranged across three hierarchical levels, allows course organisers to select the topics and to tailor their teaching materials and didactic methods according to the needs of the target audience, their prior knowledge and experience, the setting and the available time. Second, the balanced structure of the chapters and sections allows comparable teaching time to be allocated to individual units where appropriate. Third, as mentioned in Sect. 3.2, the theoretical lectures can be complemented with practical exercises to enhance participation, dialogue and interaction among trainers and learners.

However, it is crucial that teachers actually adapt the choice of topics, the level of detail, the selection of practical tasks and the time commitment to the specific situation, thereby increasing their students' attention and engagement. When designing their courses, lecturers will determine in advance what knowledge and skills their students require and select and tailor the theoretical topics, practical exercises, and literature recommendations accordingly.

The curriculum may be applied in different formats:

At its most comprehensive, it can support a complete master's degree or an intensive course delivered over several weeks. In such a format, the four sections of each chapter could be covered across four teaching blocks, with additional time allocated to selected practical exercises. In a more concise form, the curriculum could guide a short introductory course, such as a one-day overview, in which the main theoretical chapters are outlined without detailed discussion of sections and subsections, or hands-on exercises.

Another possible approach is a 'zooming' format, in which a narrow topic is placed within the broader context of PV. This may begin with an overview of the full curriculum at chapter level, followed by focused discussion of a specific chapter and section, before progressing to the subsection addressing a specific topic of special interest. Where appropriate, this may be supplemented by related practical tasks.

A further option is 'cluster teaching', in which related topics are taught together across chapters. Examples include combining 'ICSRs' with 'causality assessment' or 'signal detection' with 'real-world data'. Trainers may supplement the curriculum with locally relevant topics, such as national regulations, or serious ADRs recently reported in the lay media, to stimulate discussion and strengthen practical relevance.

Some topics are highly complex and difficult to grasp, while others evolve at a rapid pace—and often, both apply simultaneously. Examples include AI, gene therapy and medical devices.

In these cases, instructors must keep abreast of new developments in their field and ensure all parts of their courses are up to date, while simultaneously considering which sections are suitable for beginners and which are appropriate for advanced courses.

As with the previous version, this PV curriculum is a systematically structured inventory of the most important elements of PV. As such it is not a ready-to-use teaching material or a pre-defined course. Rather it can be used as a basis for the development of a range of PV courses covering most topics relevant to effective PV systems and designed for individuals with either broad or specialised areas of responsibility. It is unrealistic to expect any single PV instructor to master all aspects of the PV curriculum to the extent required to develop a full suite of courses covering every topic down to the subsection level, let alone courses on specialised subjects such as AI. Should there be a need for PV training that is both broad and in-depth, the curriculum can effectively serve as a framework for combining multiple courses taught by various specialised instructors.

Many PV trainers consider structured, modular curricula as a crucial foundation for developing context-specific courses, and many have cited our 2014 PV curriculum in this regard (e.g. [4]). Some have explicitly noted that our curriculum has proven useful in this context (e.g. [5]).

4.3 Future Updating of the Curriculum and Call for Feedback

As PV continues to evolve, regular reviewing and incorporation of emerging knowledge into the curriculum will remain necessary. Significant new developments in specific areas pose a particular challenge. This may necessitate rapid updates that potentially affect only individual chapters

or sections, along with the associated practical tasks and references.

WHO, ISoP and the authors welcome comments, suggestions and feedback from organisations, trainers and other users applying this curriculum. Such feedback will be valuable for future revisions and ensuring that the curriculum remains relevant, practical and useful for PV capacity-building.

5 Conclusions

As the climate, international relations and technologies evolve, health risks and the associated medical demands, efforts and capabilities are undergoing rapid change. These developments are associated with new medication-related risks. Fortunately, PV provides a range of ways to identify, assess and minimise these risks, and the relevant methods are continuously being further developed. To ensure that this expertise can be utilised for the benefit of patients, many healthcare workers across all levels of responsibility and regions of the world must acquire them. This, in turn, requires the provision of sufficient, high-quality, and versatile training programmes that address the individual challenges for professionals and frontline caregivers. However, course developers must be well-versed in the field of PV and able to select the right topics and tools, arrange them logically, and assign appropriate weight to each.

Like the original PV curriculum, the new version aims to support this process by organising the vast array of multifaceted elements of PV into a systematically structured toolbox. With this work WHO and ISoP drew broad-based support from experts across a wide range of regions and professional disciplines. They intend to replicate this updating periodically and in cases of special necessity. Feedback from trainers, learners and other stakeholders will help ensure that the PV curriculum remains relevant, practical and forward-looking, ultimately improving patient safety worldwide.

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