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SPECIAL ARTICLE

Teaching Pharmacovigilance: the WHO-ISoP Core Elements of a Comprehensive Modular Curriculum

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1 Introduction

The importance of pharmacovigilance (PV) for safe medicines and their safe use has increasingly been recognised during the last few years [1]. PV has been subject of intense research and regulation. In particular, it has earned more and more importance and attention in low-resource countries. This is largely due to the globalisation of trade and the availability of new, highly effective but potentially harmful chemical medicinal products in those parts of the world where traditional treatments, in particular herbal or other complementary remedies, used to prevail. A plethora of publications, guidelines and information about newly observed or further investigated adverse drug reactions (ADRs) from all over the world creates a growing burden for people working with medicines or patients to keep abreast of this development. Largely due to the global availability of information through the Internet, patients are nowadays more and more critical and often concerned about, or even frightened of, potential ADRs of their medicines. This poses an additional demand on the up-to-date capacities of their doctors and other healthcare professionals (HCPs). A particular challenge is the multidisciplinary character of PV which requires know-how in topics as different as molecular mechanisms of ADRs, clinical medicine, pharmacoepidemiology, information technology, pharmaceutical manufacturing, legal aspects, public health situations on various levels, and traditions in

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different regions of the world. Also, theoretical knowledge needs supplementing with experience and practical skills.

There are various stakeholders with specific and different interests requiring PV training, particularly industry, HCPs and their organisations, local health workers, regulators, policy makers, healthcare-related non-governmental organisations (NGOs), researchers in pharmacology or other healthcare disciplines, and teachers at universities and hospitals, both in industrialised and in developing countries. In this complex situation there is a growing need for PV capacity building, particularly by professional training through a broad range of high-quality PV courses with different focuses and different levels of detailing.

Several PV seminars and educational programmes have already been offered for many years by a range of institutions, societies and commercial entrepreneurs. Information about such courses can be readily obtained via the advertising flyers or the Internet. Such material typically outlines about 10–15 main topics and provides a few paragraphs addressing hands-on exercises, if any, together with information about the lecturers and their qualification, the duration of the course, logistic and financial aspects and the issue of homework, exams and certificates. Although there is a substantial overlap in the main topics covered by those PV courses, there are also significant differences between them. Furthermore, the descriptions of the topics, e.g. 'signal detection', are very broad. They have to be filled with detailed substance by the lecturers, reflecting their opinion of what is important, but also according to their individual expertise, preference or even personal purposes. Consequently, courses not only about PV as a whole but also about specific topics can be designed extremely differently.

For this reason, people working in public health or other fields related to drug safety, and who are responsible for teaching and who feel a need for widespread and in-depth education in this area, will often be unsure about the topics that should most importantly be covered by a course. Also, they may appreciate advice on how much time, which educational material and what kind of specific expertise of the trainers are needed so that the participants can achieve relevant knowledge and skills on defined levels. Even trainers with indisputable competence in specific areas of PV may not always present their topic within the wider context of PV, i.e. with explanation how other areas adjoin their field and how the topics relate to each other.

It is with this background that experts working in various fields of medicine safety around the world took the initiative and have co-operated to create a comprehensive, detailed and balanced curriculum of PV. Some are appointed members in PV committees associated with the World Health Organization (WHO) or work at its collaborating centres. Others are members of the Executive Committee of the International Society of Pharmacovigilance (ISoP) or its Education and Training Project (ETP) group, or work in institutions dedicated to PV. Our purpose was to provide an inventory and overview of the scope of PV, including relatively new topics such as pharmacogenomics, consumer reporting of ADRs, risk management and WHO-led international projects at several levels of specificity. It was also intended to propose a range of tasks for practical training to reinforce theoretical knowledge acquired. This paper presents the result of this work.

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2 Development of the Curriculum

The curriculum makes use of several relevant, already existing packages of topics and concepts of PV teaching. There are already well-established courses, such as those organised by the WHO collaborating centres in Uppsala [2], Rabat and Accra, the University of Hertfordshire [3], the Drug Safety Research Unit (DSRU) [4] or the London School of Hygiene and Tropical Medicine (LSHTM) [5]. Also, a teaching programme 'EU2P' is now available in the EU [6]. Furthermore, courses of general interest or with a focus on specific methods, have been offered by ISoP and the International Society of Pharmacoepidemiology (ISPE) during their annual or mid-year meetings. WHO, often in collaboration with the Uppsala Monitoring Centre (UMC) or other collaborating centres, have conducted several training courses in low- and middle-income countries in Africa, Asia and Latin America where the focus was on safety of medicines used for the treatment of important infectious diseases or on setting up new PV centres. Topics of specific relevance for industry and regulators in industrialised countries have usually been covered by the Drug Information Association (DIA) [7] and other commercial conference organisers.

The development of a core curriculum was also inspired by comprehensive overviews and textbooks, which provided ideas and information material about the broad scope of PV. For specific themes and sections, many suggestions have been retrieved from textbooks with specific focuses. Standard sources of information about specific drug-related risks include various reference books. For practical issues concerning PV within the pharmaceutical industry and their relation to drug regulatory authorities, a couple of guidelines were used as reference sources. Also, sets of specific guidance documents were consulted. Single review articles with a wide scope which seemed useful for didactical purposes, were mainly identified in the journals *Drug Safety* and *Pharmacoepidemiology and Drug Safety*. An overview of these primarily-used literature sources is given in Table 1.

For the purpose of supporting trainers and participants, a more extensive list of references has also been compiled. Many of these references are chapters of comprehensive books [8, 9], and provide overviews of the respective topic. Among journal articles, emphasis is put on systematic reviews. Guidelines and recommendations are preferably cited if they were developed by worldwide acting organisations, such as the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH). Considering public health issues relevant to low- and middle-income countries, several guidelines and recommendations are also drawn from printed material issued by the WHO and related organisations. Another selection criterion was freely available information from the Internet, particularly guidelines that are updated from time to time.

The development of the PV curriculum has been a continued effort, started by a few of us some years ago, with several additional experts subsequently contributing to the project. There was no formal procedure for reaching a consensus, such as the Delphi method; however, as many proposals as possible were taken into account.

3 Results

The curriculum presented here includes a main component consisting of modules for theoretical lecture-based training and a minor component with suggestions for hands-on exercises. The theoretical component has a hierarchical and modular structure with evenly divided tiers, and outlined in Table 2. There are 15 chapters of about equal length (hierarchy level I) with four sections each of about equal length again, making a total of 60 sections (hierarchy level II). All sections are composed of four to six subsections, i.e. approximately 300 subsections altogether (hierarchy level III).

The practical part consists of 12 times three or four proposals for hands-on exercises. These are related to, and meant to illustrate and provide actual application of, know-how obtained from lectures about those theoretical topics for which skills and experience seem helpful or even necessary. This applies to the fields covered by chapters 4–15. Proposals for practical tasks related to chapters 1–3 are intentionally not included because it was felt that learning of these parts is almost entirely based on the acquirement of theoretical knowledge. The practical part is described in Table 3.

The comprehensive list of references is available in the electronic supplementary material.

4 Discussion

4.1 Contents and Structure of the Curriculum and its Relation to Established Pharmacovigilance Courses

Our curriculum provides comprehensive coverage of almost all areas of PV, i.e. biochemical, clinical, regulatory and methodological aspects. It also addresses issues relevant for highly industralised and low industrialised countries, including their different healthcare structures and issues. Thus, there are topics as heterogeneous as genetic testing, risks related to monoclonal antibodies, adverse events following immunisation (AEFIs), counterfeiting, record linkage, periodic safety update reports and communication to HCPs.

Table 1 Tabulated overview of primarily-used literature sources

Literature category	Author(s), editor(s)	Title	References
Textbooks on the broad field of pharmacovigilance	Talbot J, Aronson JK (eds.)	Stephens' detection and evaluation of adverse drug reactions	[8]
	Andrews E, Moore N (eds.)	Mann's pharmacovigilance	[9]
Textbooks on specific aspects of pharmacovigilance	Strom BL, Kimmel SE, Hennessy S (eds.)	Pharmacoepidemiology	[10]
	Van Boxtel CJ, Santoso B, Edwards IR (eds.)	Drug benefits and risks	[11]
	Rawlins MD	Therapeutics, evidence and decision-making	[12]
Reference books	Aronson JK (ed.)	Meyler's side effects of drugs	[13]
	Sweetman SC (ed.)	Martindale - the complete drug reference	[14]
	World Health Organization	WHO model formulary	[15]
Compilations of guidances	CIOMS - Council for International Organizations of Medical Sciences	Publications on drug development and use	[16]
	ICH - International Conference on Harmonisation	Guideline index batch E	[17]
	ENCePP - European Network of Centres for Pharmacoepidemiology and Pharmacovigilance	ENCePP guide on methodological standards in pharmacoepidemiology	[18]
	EMA - European Medicines Agency	Good pharmacovigilance practices	[19]
	MHRA - UK Medicines and Healthcare products Regulatory Agency	Good pharmacovigilance practice guide	[20]
	US FDA - Food and Drug Administration	Guidance, compliance and regulatory information: drug safety	[21]
	Cobert B	Cobert's manual of drug safety and pharmacovigilance	[22]
	University of Ghana Medical School	WHO's PV Toolkit	[23]
	WHO Department of Essential Medicines and Healthcare Products	Publications on pharmacovigilance	[24]
	ISPE - International Society of Pharmacoepidemiology	Guidelines for good pharmacoepidemiology practices	[25]
Review articles in journals		Drug Safety - official journal of the International Society of Pharmacovigilance	[26]
		Pharmacoepidemiology and Drug Safety - official journal of the International Society of Pharmacoepidemiology	[27]

The curriculum as such is neither ready-for-use teaching material nor the description of a course. It just reflects the current status of the rapidly evolving science in PV. Accordingly, it needs continuous updating and, therefore, regular consideration of new or updated information and guidelines is essential. The theoretical part formulates headings and key terms of topics which a trainer should address in order to cover the essential scope of PV, and provides a harmonised structure for the material. It remains up to the lecturer to develop details, texts and slides, real-life cases or scenarios, and other didactic materials. Likewise, the proposals for hands-on exercises are frameworks that would need to be filled with concrete teaching material and explicitly formulated tasks, selected to be of relevance to the audience, e.g. in a particular geographical region. Trainers may find help in the detailed background information provided in the complete reference list. The selected literature (see electronic supplementary material) provides more information than just the basics of PV, and explains in detail most of the important topics.

Even though some of the broad headings of chapters are similar to those of the well-established courses mentioned previously, our curriculum appears to be rather unique in its granularity of key topics, detailed at a three-level hierarchy, for advanced, medium and basic 'knowledge' modules, as well as for hands-on exercises. Another advantage of our curriculum resides in its broad and impartial basis of competence through the involvement of many PV experts from international non-governmental not-for-profit organisations which we consider representative for all major fields of PV.

The strict hierarchical and modular structure may seem too rigid to some PV experts; we are well aware of the fact

Table 2 Core elements of the modular pharmacovigilance curriculum for lecture-based teaching

1	**What is and Why do we Need Pharmacovigilance (PV)?**
1.1	**Subject and scope of PV**
1.1.1	Context, definition and purpose of PV
1.1.2	The adverse event (AE) and adverse drug reaction (ADR) at the centre of PV
1.1.3	The wide scope of PV
1.1.4	Persons and parties involved in PV–their concerns, competences and interactions
1.1.5	The increasing complexity and challenges of PV
1.2	**History of PV: important ADRs and methodological and organisational developments**
1.2.1	The origin of modern PV: thalidomide and the emergence of ADR reporting and drug legislation
1.2.2	Major disasters and their impact on PV: OCs–VTE, HRT–breast cancer, cerivastatin–rhabdomyolysis, coxibs–cardiovascular death, etc
1.2.3	The shaping of institutions, international cooperation and information exchange
1.2.4	Focus on methods: spontaneous reporting, pharmacoepidemiology, data bases and linkage, data mining, genetic testing
1.2.5	Focus on medication errors, counterfeiting and patient safety
1.2.6	Focus on proactive risk management and legislation
1.3	**ADRs and public health**
1.3.1	Effects of ADRs in general for patients' health and treatment and for drug development and acceptance
1.3.2	High risk patient groups, drug groups and settings
1.3.3	Statistics of drug-related harm to patients' treatment, health and life
1.3.4	Statistics of financial and other resources needed due to drug-related harm
1.3.5	Statistics of wrong medication leading to drug-related harm
1.3.6	Ecological consequences of drug disposal
1.4	**Limited risk prediction from molecular analogy, pre-clinical studies and pre-marketing clinical trials**
1.4.1	Risk prediction by drug class analogy
1.4.2	Pre-clinical in vitro tests
1.4.3	Animal toxicology, concept and options
1.4.4	Animal toxicology, limitations
1.4.5	Pre-marketing clinical trials, concept, options, limitations
2	**Fundamental Clinical Aspects of ADRs**
2.1	**Types and mechanisms of ADRs**
2.1.1	'Type A' (pharmacological): exaggeration of desired effect or effect at different site or of different type
2.1.2	'Type B' (hypersusceptibility/idiosyncratic)
2.1.3	Other types of ADRs: poisoning, drug resistance or dependence, carcinogenic or teratogenic effect, infection
2.1.4	Other ADR classifications: according to time course, dosage, patient susceptibility, mechanism, expectedness
2.1.5	Seriousness and severity of ADRs
2.1.6	Surrogate markers as diagnostic indicators, non-serious ADRs or precursors of serious ADRs
2.2	**Pharmacogenetic causes of inter-individual variability in the susceptibility to ADRs**
2.2.1	Definition, biochemical basis, scope and challenges of pharmacogenetics
2.2.2	Genetic polymorphism of enzymes involved in phase I drug metabolism: CYP 1, 2 and 3 oxygenases
2.2.3	Genetic polymorphism of enzymes involved in phase II drug metabolism and in drug transport
2.2.4	Genetic polymorphism of ion channels, receptors and enzymes involved in pharmacodynamics
2.2.5	Genetic polymorphism of genes responsible for immunological and other idiosyncratic Type B ADRs
2.2.6	Drug development and genetically individualised treatment: tailored indications, tests, safeguards
2.3	**Non-genetic risk factors for ADRs and complex interactions**
2.3.1	Young and old age, gender, social factors
2.3.2	Target- and concomitant diseases including virus infection, history of drug intolerance, temporary situations
2.3.3	Pregnancy and teratogenic effects
2.3.4	Drug–drug interactions at same molecule/site–pharmacokinetic or pharmacodynamic, synergistic or antagonistic
2.3.5	Complex interactions between drugs affecting different molecular sites or organs and other risk factors, e.g. renal or hepatic impairment
2.3.6	Drug interactions with food, alcohol, grapefruit, vitamins as food additives, smoking, sun exposure

Table 2 continued

2.4	**Clinical management of ADRs**
2.4.1	Avoiding ADRs of individual patients à priori: personal risk assessment and precautionary measures
2.4.2	Treating symptoms and assessing and eliminating possible causes in case of ADR suspicion
2.4.3	Identifying the 'culprit' in case of ADR suspicion
2.4.4	Continuing treatment after an ADR was considered likely
3	**Important ADRs and 'Risk Driving' ADRs of Important Medicines**
3.1	**Serious ADRs at organ classes where 'Type B' reactions are important. Most involved drugs**
3.1.1	ADRs affecting the skin
3.1.2	ADRs affecting haematopoiesis, blood cells and haemostasis
3.1.3	ADRs affecting the liver and the biliary system
3.1.4	ADRs affecting the kidney and urinary tract
3.1.5	ADRs affecting the respiratory tract
3.2	**Important ADRs at organ classes where 'Type A' reactions are most important, and the mostly involved drugs**
3.2.1	ADRs affecting the gastrointestinal tract
3.2.2	ADRs affecting the endocrine system and metabolism
3.2.3	ADRs affecting the cardiac and the vascular system
3.2.4	ADRs affecting the nervous system
3.2.5	ADRs affecting vision, hearing and taste
3.2.6	Tumorigenic and teratogenic effects
3.3	**Focus on ADRs of anti-infectives particularly important in limited resource settings and of vaccines**
3.3.1	ADRs of anti-HIV medicines
3.3.2	ADRs of anti-tuberculosis medicines
3.3.3	ADRs of anti-malaria medicines
3.3.4	ADRs of medicines used in neglected tropical diseases
3.3.5	Vaccines: peculiarities of their ADRs in general, lack of effectiveness, injection site reactions
3.3.6	Vaccines: generalised ADRs due to immunological reactions, toxicity or replication of infective agents
3.4	**'Risk drivers' of important drugs for common illness and chronic diseases, biologicals, herbals**
3.4.1	ADRs of medicines used in common cold (fever, headache, pain, cough)
3.4.2	ADRs of medicines used in respiratory disorders (asthma, COPD)
3.4.3	ADRs of medicines used in rheumatic disorders (back pain, osteoarthritis)
3.4.4	ADRs of medicines used to treat anxiety, depression and mental discomfort
3.4.5	ADRs of medicines used in metabolic syndrome (hypertension, dyslipidaemia, obesity, diabetes)
3.4.6	ADRs of widely used herbals
4	**'Individual Case Safety Reports' ('ICSRs')**
4.1	**Concerns about ADRs: medical, psychological and regulatory background and reasons for reporting**
4.1.1	Definition of ICSRs and their 'typology' with respect of provenance and subject matter
4.1.2	Place value of ICSRs in PV: insights they can and cannot provide and their impact on drug regulation
4.1.3	Healthcare professionals as reporters: their knowledge, diagnostic means, motivations and fears
4.1.4	Patients as reporters: their concerns, expectations, specific knowledge and observations
4.1.5	MAHs as reporters: their information background, sources and obligations
4.1.6	'Culture', stimulation and organisation of spontaneous ADR detection and reporting
4.2	**Contents, structure and validity of reports and reporting procedures**
4.2.1	Minimum necessary information, structured fields on one-page reporting forms, overview of ICH E2B
4.2.2	Case narratives
4.2.3	Case follow-up and validation
4.2.4	Literature reports
4.2.5	Use of AE/ADR terminologies and definitions and drug dictionaries by primary reporters
4.2.6	Use of technical means for reporting

Table 2 continued

4.3	**Case assessment**
4.3.1	Completeness, accuracy and precision of the report
4.3.2	Certainty of the diagnosis
4.3.3	Seriousness and severity of the AE/ADR
4.3.4	Causality of the AE: purpose, criteria and problems of the assessment
4.3.5	Causality of the AE: common general and specific assessment methods, outcome ratings, shortcomings
4.3.6	Expectedness of the AE/ADR
4.4	**Reports related to vaccines, herbals and specific situations**
4.4.1	Reports about adverse events following immunisation (AEFI): specific features
4.4.2	Causality assessment with AEFI
4.4.3	Reports about AEs/ADRs with herbal medicines
4.4.4	Reports about AEs/ADRs related to pregnancy and lactation
4.4.5	Reports about drug-drug interactions, drug abuse and poisoning
5	**Pharmacovigilance in Clinical Trials**
5.1	**Characteristics of pharmacovigilance in clinical trials**
5.1.1	Types, objectives and limitations of pre-authorisation studies
5.1.2	Categories of primary hazard data
5.1.3	Safety in focus of early drug development, in particular first-into-man studies
5.1.4	Prevailing patient groups and medicines according to current public health needs
5.1.5	Persons and bodies involved, responsibilities, co-operation
5.2	**Collection of hazard data: planning and practical realisation**
5.2.1	Study protocol, investigator brochure, informed consent form
5.2.2	Specific vulnerable (sub-) populations
5.2.3	Treatment-related risks
5.2.4	Test parameters
5.2.5	Strategies of data collection
5.2.6	Data presentation
5.3	**Risk assessment**
5.3.1	Assessment of individual AE observations
5.3.2	Detection of specific ADRs as harmful properties of IMPs and non-IMPs
5.3.3	Statistical quantification of safety data from individual studies
5.3.4	Data pooling and ADR frequency estimation
5.3.5	Development of labelling
5.4	**Guidance and regulatory framework**
5.4.1	Guidelines and directives
5.4.2	Key documents at the start and during a study
5.4.3	Key documents at and after the end of a study
5.4.4	Reporting obligations
5.4.5	Other communication activities
6	**Counterfeiting, Quality Defects and Medication Errors**
6.1	**Counterfeiting, demarcation against manufacturing-related quality defects**
6.1.1	Definition of substandard/spurious/falsely labelled/falsified/counterfeit (SSFFC) medicines and respects of counterfeiting
6.1.2	Pattern and scale of counterfeiting; consequences, in particular antimicrobial resistance
6.1.3	Methods used by counterfeiters
6.1.4	Technical, organisational and political anti-counterfeit measures
6.1.5	How the legitimate MAH can and should help
6.1.6	How to manage unintentional quality defect problems

Table 2 continued

6.2	**Medication error (ME): definition, impact, detection**
6.2.1	Definition and typology of MEs, demarcation from off-label use
6.2.2	ME statistics and impact on public health
6.2.3	Victims, medical situations and medications typical for MEs
6.2.4	Detection of MEs: national spontaneous reporting schemes for professionals
6.2.5	Detection of MEs: methods in specific healthcare settings for professionals
6.2.6	Detection of MEs: patient reporting
6.3	**ME reports: description and assessment**
6.3.1	Description of clinical patient aspects
6.3.2	Description of procedural and patient adherence aspects
6.3.3	Assessment of the proximal/immediate cause
6.3.4	Contributing system factors
6.3.5	Root cause analysis (RCA)
6.3.6	Assessment of avoidability/preventability
6.4	**Preventive measures**
6.4.1	Education and information material
6.4.2	Culture of the handling of ME incidences and learning from them
6.4.3	Global political and regulatory activities
6.4.4	Local and technical organisational measures
6.4.5	Specific aspect: conflict, synergy and harmonisation with classical PV (challenges)
6.4.6	Legal, ethical and confidentiality aspects
7	**Spontaneous ICSR Reporting Systems (SRS)**
7.1	**Definition, settings, potential and limitations of SRS**
7.1.1	Definition, potential and achievements of SRs
7.1.2	SRS settings and resources; sources of spontaneous reports (SRs)–healthcare professionals (HCPs), patients, companies, media
7.1.3	Detecting, documenting and reporting of AEs/ADRs: methods, forms, routes, software
7.1.4	Places and institutions collecting spontaneous reports
7.1.5	Informational limitations of SRs: incomplete, no denominator, biases; proposed caveats
7.1.6	Stimulated, mandatory, solicited and targeted reporting
7.2	**Computerised ICSR databases: requirements and structure, administration**
7.2.1	Typical ICSR databases: relational model, SQL language
7.2.2	Structure (e.g. separate patient, literature, study reports), scalability, performance
7.2.3	Stability, resilience, security, storage, maintenance
7.2.4	Database management systems: requirements, available report management software
7.2.5	Quality assurance: duplicate-, syntax-, coherence-check, tracking facilitation and follow-up
7.2.6	Specific requirements of pharmaceutical company databases, e.g. reporting functions
7.3	**Data transmission and entry**
7.3.1	Forms and formats of ICSR transmission: one-page forms, email, phone, ICH E2B, ICH M2
7.3.2	Coding of diseases and ADRs using terminologies WHO-ART, ICD, MedDRA
7.3.3	Coding of drugs using classifications and dictionaries: ATC, WHO-DD (enhanced), EVMPD
7.3.4	Special issues: quality check, anonymisation, case IDs, lab data tables, narratives, language
7.3.5	Correspondence with reporters: confirmation of receipt, requests for additional data
7.4	**Data retrieval, descriptive statistics, access and confidentiality**
7.4.1	Electronic techniques of data retrieval: formats, networks, browsers and other tools, SGML language
7.4.2	Serving the searcher: standardised entry screens, search support, stratification of data
7.4.3	Descriptive statistics (presenting numbers; not analysing and testing)
7.4.4	Format of retrieval results: line listings, summary tabulations, profiles, sometimes ICSRs
7.4.5	Graded access according to data and interested parties, proactive publications; confidentiality
7.4.6	Important accessible databases, terms of access: WHO/UMC, others

Table 2 continued

8	**Signal Detection and Management**
8.1	**Definition of a signal; sources, potentials, detection by non-statistical medical means**
8.1.1	What is a 'signal'?–definitions by WHO, CIOMS, others
8.1.2	What a signal may indicate: new ADR, higher severity or frequency, risk factors, wrong medication, product faults
8.1.3	Sources of information which may constitute a signal: ADR databases, case-control surveillance, other sources
8.1.4	Basic requirements for signal detection and management
8.1.5	Stakeholders in the signal detection and management process
8.1.6	Detection of signals for new ADRs from ADR case-series by non-statistical medical means
8.2	**Disproportionality statistics for signal detection in spontaneous ISCR databases**
8.2.1	Principles of statistical data mining in ICSR databases
8.2.2	Calculating proportional reporting ratios (PRRs) and reporting odds ratios (RORs)
8.2.3	Bayesian methods: information component (IC) and gamma poisson shrinker calculating EBGM
8.2.4	Calculating statistical significance of disproportionate reporting and confidence intervals
8.2.5	Determining sensitivity and specificity of signal detection by defining minimum number of reports, extent of disproportionality and statistical significance
8.2.6	Strengths and weaknesses of different data mining methods, e.g. vulnerability to low and high numbers
8.3	**Special issues in disproportionality approaches**
8.3.1	Applying disproportionality statistics to ICSRs selected by quality, ADR (group), drug (class), indication, age. Excluding known ADRs
8.3.2	Detecting complex associations: drug-drug interactions, other risk factors, syndromes
8.3.3	Combining ICSR and drug utilisation data (e.g. from IMS) as denominator
8.3.4	Applying disproportionality statistics to longitudinal patient record and exposure data
8.3.5	Sequential probability ratio tests (SPRTs); tree-based scan statistic (ScanTree)
8.3.6	Available software for data mining
8.4	**Prioritisation, validation, assessment, risk confirmation or refusal, communication, further action**
8.4.1	Prioritisation according to evidence and potential public health impact (seriousness, drug utilisation)
8.4.2	Validation by checking report quality, duplicates, plausibility, consistency, other information, biases
8.4.3	Assessment, absolute: clinically plausible causality, meaning, impact, preventability
8.4.4	Assessment, relative: relating number of reports to utilisation, comparing with other drugs
8.4.5	Consequences of confirmed signals: communication, further investigation, options of action
9	**Post-Authorisation Observational Studies and Clinical Trials in PV**
9.1	**Definition and objectives of post-authorisation studies, general requirements, specific studies**
9.1.1	Definition of post-authorisation studies, non-interventional studies, pharmacoepidemiology
9.1.2	Post-authorisation studies for confirmation of signals and providing data on ADR frequency and causality
9.1.3	Observational studies: general formal and scientific requirements, opportunities, limitations
9.1.4	Population-oriented post-authorisation studies: disease studies, drug utilisation studies
9.1.5	Post-authorisation randomised clinical trials, in particular 'large simple trials' (LSTs)
9.2	**Important observational studies and their strengths and weaknesses**
9.2.1	Cohort studies in general: design, conduct, statistical analysis and presentation of results
9.2.2	Cohort-event monitoring (CEM), including PEM as specific applications
9.2.3	Dealing with different hazard functions and different exposure times (person years)
9.2.4	Case-control studies: design (including nested in cohorts), conduct, statistical analysis and presentation of results
9.2.5	Rationale and approaches for within-patient study designs, e.g. case-crossover studies
9.3	**Bias, confounding and effect modification in observational studies**
9.3.1	Definition of bias and confounding and principles of dealing with them
9.3.2	Important biases: selection (e.g. referral) bias, information (e.g. recall) bias, detection bias; how to deal with these biases
9.3.3	Important confounders, in particular confounding by indication
9.3.4	How to deal with these confounders (e.g. matching, propensity scoring, sensitivity analysis)
9.3.5	Effect modification: principles of measurement and presentation in a study report
9.3.6	Novel designs avoiding with these problems: within-subject or case-crossover designs

Table 2 continued

9.4	**Sources of study subjects and data**
9.4.1	De novo data collection (interviews, patient charts), spontaneous reports, surveys, CEM
9.4.2	Large automated health databases (LADs) or electronic medical records: typical structure
9.4.3	Important accessible LADs in North America, Europe and Asia
9.4.4	Registers of diseases, specific ADRs or exposure; pregnancy registers
9.4.5	Record linkage: options and problems (e.g. compatibility, confidentiality)
9.4.6	Choosing data and methods for the estimation of ADR frequencies
10	**Benefit-Risk Assessment**
10.1	**'Benefit-risk': definitions, methodological approaches; disease as criterion of benefit**
10.1.1	Definition of benefit, harm, chance, risk and their components magnitude, duration, likelihood
10.1.2	Initiatives to develop methods for benefit-risk assessment: PROTECT, BRAT
10.1.3	Frameworks for benefit-risk analysis: Ashby-Smith Bayesian approach, MCDA, SMAA
10.1.4	Complexity of disease-related risks: multiplicity, time dependence, likelihood, subjectivity
10.1.5	Disease-related harm and risk as targets of drug treatment and criteria of benefit and chance
10.2	**Drug-related risks (ADRs): analysing, weighting and combining their components**
10.2.1	Complexity of ADR-related risks: multiplicity, time dependence, likelihood, subjectivity
10.2.2	Measuring and weighting disease- and drug-related objective and subjective 'instantaneous harm'
10.2.3	Considering aspects of time: point in time (hazard function), duration of harm
10.2.4	Combining harm and likelihood: the risk (due to drugs as well as diseases)
10.2.5	Weighting, combining, comparing risks using single metrics, or 'currencies', and 'risk equivalents'
10.2.6	Typical discrete and continuous measures of harm: deaths, incidents, hospitalisations, QALYs, etc.
10.3	**Balancing benefit/chance vs. harm/risk and comparing different treatment options**
10.3.1	Principles of estimating benefit/chance in terms of reducing disease-related harm/risk using single metrics
10.3.2	Expressing benefit/chance and risk using indices like NNTand NNH, adjusted for utility, if applicable
10.3.3	Using the semi-quantitative Markov and Kaplan–Meier methods, including aspects of time
10.3.4	Estimating the difference between risks from untreated disease and treated disease plus ADRs; calculating the INHB
10.3.5	Comparing those differences across alternative treatment options: 'indirect/mixed treatment comparisons'
10.3.6	Combining and balancing disease-related harm/risks and drug-related benefit/chance and ADRs on the public health level
10.4	**Taking into account preferences of stakeholders, uncertainties and options for actions**
10.4.1	Determining preferences vs. benefit/chance and harm/risk of different stakeholders: preference values; utility surveys
10.4.2	Non-pharmacological and indirect risks: misuse, errors, further complications
10.4.3	Options for improving the chance-risk balance and their likely impact; aspects of feasibility
10.4.4	Uncertainties in the underlying data: level of evidence, confidence intervals; applying the Probabilistic Simulation Method (PSM)
10.4.5	Analysing sensitivity: worst case–best case scenarios; considering the precautionary principle
10.4.6	Making chance-risk estimates understandable: visualisation and communication
11	**Pharmacovigilance and Risk Management Systems, Risk Management Plans (RMPs), Inspections**
11.1	**Pharmacovigilance systems: definition, stakeholders and operation**
11.1.1	Definition and elements
11.1.2	Contents of the 'Pharmacovigilance System' document, masterfile concept
11.1.3	Pharmacovigilance systems of pharmaceutical companies, marketing authorisation holders (MAHs) and distributors
11.1.4	Pharmacovigilance systems of regulatory authorities
11.1.5	Standard operating procedures (SOPs)
11.1.6	Maintenance of the pharmacovigilance systems
11.2	**Product-related risk management systems**
11.2.1	Rationale for establishing risk management systems and objectives
11.2.2	Establishing a risk management system: starting point and responsibilities
11.2.3	Characterisation of the risk profile
11.2.4	Risk management during the lifecycle of a drug, planning of PV activities, updating the risk management system
11.2.5	Legal basis and guidelines, role of relevant stakeholders and partners

Table 2 continued

11.3	**Specific product-related RMPs; other tools and activities**
11.3.1	Scope, definitions and responsible persons and institutions to establish risk management tools: RMP, REMS, others
11.3.2	Elements of risk management tools: safety specification, pharmacovigilance plan, risk mitigation measures; SmPC and PIL
11.3.3	When to establish and update a risk management tool and pharmacovigilance plan
11.3.4	Implementation, monitoring and assessing effectiveness of risk mitigation measures
11.3.5	Communication
11.4	**Pharmacovigilance inspections and audits, quality assessment**
11.4.1	Purpose, frequency and actors
11.4.2	Indicators of capacity and performance of the pharmacovigilance system
11.4.3	External inspections by competent authorities
11.4.4	Internal audits in companies and regulatory authorities
11.4.5	Quality assurance and benchmarking processes
11.4.6	Legislation and guidelines
12	**Industry and Regulatory Authorities, Mandatory Procedures from Legislation**
12.1	**Facilities at pharmaceutical companies, marketing authorisation holders, wholesalers and distributors**
12.1.1	Pharmacovigilance system and SOPs, crisis management plan
12.1.2	QPPV, staff resources (scientific and administrative), financial resources, technical equipment
12.1.3	Databases (ADR reports), performance tools, statistical tools and methods for analyses
12.1.4	Product-related archives, correspondence archives, library and access to electronic literature databases
12.1.5	Communication tools, contact details, Internet access, fax, phone, video conference services
12.2	**Mandatory tasks and procedures from legislation at industry**
12.2.1	ADR collection and reporting to competent authorities, signal detection and management
12.2.2	Study reports, Periodic Safety Update Reports (PSURs), Periodic Benefit Risk Evaluation Reports (PBRERs)
12.2.3	Other documents: DSUR; RMP, REMS; renewal dossiers; reports on request
12.2.4	Regular benefit/chance-to-harm/risk assessment
12.2.5	Decision making, monitoring effectiveness of measures taken
12.2.6	Quality management, determination and assessment of performance indicators, training
12.3	**Facilities at regulatory authorities**
12.3.1	Pharmacovigilance system and SOPs, crisis management plan
12.3.2	Staff resources (scientific and administrative), technical equipment
12.3.3	Databases (ADR reports), statistical tools and methods for analyses
12.3.4	Product-related archives, correspondence archives, library and access to electronic literature databases
12.3.5	Communication tools, press officer, contact details, Internet access, fax, phone, video conference service
12.3.6	Quality management, determination and assessment of performance indicators, training
12.4	**Mandatory tasks and procedures from legislation at regulatory authorities**
12.4.1	ADR collection and storing in an electronic database, signal detection and management
12.4.2	Causality assessment and root cause analysis, regular benefit/harm-to-harm/risk assessment
12.4.3	Decision-making processes, monitoring effectiveness of measures taken
12.4.4	Reporting to other competent authorities, international organisations and governments
12.4.5	Quality management system, training
12.4.6	Communication
13	**PV Organisation and Public Health**
13.1	**Detection, documentation and reporting of ADRs on the local level**
13.1.1	Reality in rural areas in limited resource settings: patients, diseases, drugs, distributors, HCPs and other health workers
13.1.2	Symptoms of what could be ADRs of drugs used in tropical and other serious infections
13.1.3	What normally happens in the first instance if a patient suffers from such an experience
13.1.4	ADR reporting in industrialised countries on the local level: persons, tools, communication
13.1.5	Industry and drug marketing persons/institutions in ADR reporting in poor and rich settings
13.1.6	Use of e-technology (mobile phones, apps, company websites)

Table 2 continued

13.2	**PV capacity building and organisation on the regional and national level**
13.2.1	A national PV policy and legislation
13.2.2	National and regional PV centres and networks; staff, technical equipment, library
13.2.3	System and tools for spontaneous ADR reporting
13.2.4	Concepts for PV capacity building within a centre or health facility, training
13.2.5	Realisation of PV capacity: budget, funds, donors
13.2.6	Co-operation with HCPs, hospitals, professional societies, academia, patient organisations, industry on national and international level
13.3	**Public Health Programmes (PHPs) with PV aspects and other PV projects**
13.3.1	Major elements of PHPs; WHO as initiator, organiser and co-ordinator of PHPs; co-operation with national regulatory authorities
13.3.2	Tasks and tools related to PV in PHPs: ethnically and socially specific ADRs; CEM, TSR
13.3.3	Important PHPs targeted at AIDS, tuberculosis, malaria: GFATM, BMGF, UNITAID
13.3.4	Vaccination programmes
13.3.5	Other international PV projects: ENCePP, PROTECT, OMOP, MIHARI, 'Monitoring Medicines' project
13.3.6	Evaluation of PV data in the context of PHPs
13.4	**Co-operative international organisations, industry associations**
13.4.1	WHO, WHO Collaborating Centres–Uppsala, Accra, Rabat; ACSoMP, GACVS; CIOMS; regional organisations and initiatives
13.4.2	Patient safety organisations: WAPS, IAPO, EURODIS
13.4.3	International Society of Pharmacovigilance (ISoP), ISPE, IUPHAR
13.4.4	International Conference on Harmonisation (ICH), procedures, deliverables and publications
13.4.5	Mainly pharmaceutical industry: DIA, IFPMA
13.4.6	International Organisation for Standardisation (ISO)
14	**Communication**
14.1	**Context and guidance**
14.1.1	Public health goals
14.1.2	Scene and climate
14.1.3	Theories and guidance
14.1.4	Legal framework
14.1.5	Experience on communication effectiveness
14.1.6	Crisis management
14.2	**Communication with patients and healthcare professionals: tools, channels and processes**
14.2.1	Individual communication
14.2.2	Mass communication
14.2.3	Involvement of the public
14.2.4	Tools and channels
14.2.5	Impact, feedback and evaluation
14.3	**Communication with patients and healthcare professionals: contents and presentation**
14.3.1	Considering the target population
14.3.2	Typical subject matters and recommendations to patients and healthcare professionals
14.3.3	Selection of data
14.3.4	Information elements and structure of the text
14.3.5	Specific medications and hazards
14.4	**Interaction among stakeholders, including the media**
14.4.1	Communication for involvement of the public in PV processes
14.4.2	Interactions between stakeholders throughout the communication process
14.4.3	Interaction between stakeholders in relation to RMPs
14.4.4	Specifics for interaction with scientific and general media
14.4.5	Press conferencing

Table 2 continued

15	**Sources of Information**
15.1	**Primary data: figures, facts, terms, cases**
15.1.1	Databases with spontaneous ADR reports
15.1.2	Data from poison control centres: intoxication, contamination
15.1.3	Public health data, epidemiological databases
15.1.4	Sales and exposure data, drug utilisation data
15.1.5	Thesauruses and dictionaries of ADR terms, diseases, drugs
15.2	**Secondary information: assessments, judgements, decisions (hardcopy or electronic version)**
15.2.1	Study results, ICSR observations, summary assessments
15.2.2	Guidelines, specific recommendations
15.2.3	Drug monographs, regulations, other official decisions
15.2.4	International symposia, local news and advisories
15.2.5	Mixed information, including news, policy, economy, announcements
15.3	**Electronic/Internet methods for searching and managing information**
15.3.1	Gateways to literature databases
15.3.2	Search engines and attention tools
15.3.3	Software for ADR database searching
15.3.4	Shared networks, discussion groups, chatrooms, weblogs, social media
15.3.5	Services for literature search and drug information management
15.3.6	Strategies for searching for information and literature management
15.4	**Materials and training courses, where appropriate, specific for regions or settings**
15.4.1	Textbooks
15.4.2	Courses: general or specific methodological (ICSR assessment, signal detection, pharmacoepidemiological studies)
15.4.3	Courses: technical/administrative/procedural topics (e.g. electronic reporting, literature search, PBRERs)
15.4.4	Courses: specific medical topics (e.g. vaccines, anti-HIV drugs, anti-malarials; hepatotoxicity)
15.4.5	'Hands-on' practical training

ACSoMP (WHO) Advisory Committee on Safety of Medicinal Products, *ADR* adverse drug reaction, *AE* adverse event, *AEFI* adverse event following immunisation, *ATC* Anatomical Therapeutic Chemical classification system, *BMGF* Bill and Melinda Gates Foundation, *BRAT* Benefit-Risk Assessment Team, *CEM* cohort event monitoring, *CIOMS* Council of International Organizations for Medical Sciences, *COPD* chronic obstructive pulmonary disease, *CYP* cytochrome P450, *DIA* Drug Information Association, *DSUR* Development Safety Update Report, *EBGM* empirical Bayes geometric mean, *EMA* European Medicines Agency, *ENCePP* European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, *EURODIS* Rare disease patients in Europe, *EVMPD* EudraVigilance Medicinal Product Dictionary, *GACVS* Global Advisory Committee on Vaccine Safety, *GFATM* Global Fund for AIDS, Tuberculosis and Malaria, *HCP* healthcare professional, *HRT* hormone replacement therapy, *IAPO* International Alliance of Patients' Organizations, *IC* information component, *ICD* International Classification of Diseases, *ICH* International Conference on Harmonization, *ICH E2B* guideline no. E2B of the International Conference on Harmonisation, *ICH M2* guideline no. M2 of the International Conference on Harmonisation, *ICSRs* individual case safety reports, *IDs* identification data, *IFPMA* International Federation of Pharmaceutical Manufacturers and Associations, *IMP* investigational medicinal products, *IMS* international medical statistics, *INHB* incremental net health benefit, *ISO* International Organisation for Standardisation, *ISoP* International Society of Pharmacovigilance, *ISPE* International Society for Pharmacoepidemiology, *IUPHAR* International Union of Basic and Clinical Pharmacology, *LAD* large automated health database, *LST* large simple trial, *MAH* marketing authorisation holder, *MCDA* multi-criteria decision analysis, *ME* medication error, *MedDRA* Medical Dictionary for Regulatory Activities, *MIHARI* Medical Information for Risk Assessment Initiative, *NNH* number needed to harm, *NNT* number needed to treat, *OC* oral contraceptive, *OMOP* Observational Medical Outcomes Partnership, *PBRER* periodic benefit risk evaluation report, *PEM* prescription event monitoring, *PHPs* Public Health Programmes, *PIL* Patient Information Leaflet, *PROTECT* Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, *PRR* proportional reporting ratio, *PSUR* periodic safety update report, *PV* pharmacovigilance, *QALY* quality-adjusted life year, *QPPV* qualified person for pharmacovigilance, *RCA* root cause analysis, *REMS* risk evaluation and mitigation strategy, *RMP* risk management plan, *ROR* reporting odds ratio, *SGML* Standard Generalised Makeup Language, *SMAA* stochastic multi-criteria acceptability analysis, *SmPC* summary of product characteristics, *SOP* standard operating procedure, *SPRT* sequential probability ratio test, *SQL* structured query language, *SR* spontaneous report, *SRS* spontaneous reporting system, *SSFFC* substandard/spurious/falsely labelled/falsified/counterfeit, *UMC* Uppsala Monitoring Centre, *VTE* venous thromboembolism, *WHO-ART* WHO Adverse Reaction Terminology, *WHO-DD* WHO Drug Dictionary, *TSR* targeted spontaneous reporting, *WAPS* World Alliance for Patient Safety, *WHO* World Health Organization

Table 3 List of suggested practical tasks for hands-on exercises as part of the pharmacovigilance curriculum

4P	**'Individual Case Safety Reports' ('ICSRs') - assessment and creation of a report**
4P1	Assess an ICSR about a serious AE related to a drug used in a serious disease where co-medication and other risk factors could have contributed and documentation is poor
4P2	Assess an AEFI case report for seriousness, expectedness, correctness of vaccination, risk factors, causality, preventability
4P3	Create an ICSR considering a serious AE related to a herbal medicine: use or design an appropriate form, enter data into fixed fields, write a narrative
5P	**Pharmacovigilance in clinical trials: assessment and creation of documents**
5P1	Assess the risk-relevant part of a given informed consent form for participants in a large simple trial with respect to relevance, completeness and understandability
5P2	Assess a given DSUR considering a new biotechnological medicine with respect to flaws, gaps and strengths
5P3	Assist a fictitious patient in reporting a serious AE using the recommendation of the Patient Reported Outcomes Safety Event Reporting Consortium (PROSPER)
6P	**Counterfeiting, quality defects and medication errors: proposal of analysis and action**
6P1	Propose appropriate actions in a poor resource setting scenario where patients unexpectedly did not respond to an antibiotic, and counterfeiting or new bacterial resistance is suspected
6P2	Outline a root cause analysis of a real or fictitious drug-related disaster to which several sequential direct and indirect causes might have contributed
6P3	Create an Ishikawa-Fishbone diagram, a Swiss-Cheese-Barrier diagram or a 'Management Oversight and Risk Tree' for the scenario outlined under 6P2
7P	**Spontaneous ICSR reporting systems: entering ICSRs into, and retrieval from, the database**
7P1	Code an ICSR data using ADR terms and drug thesauruses (MedDRA, WHO-ART, WHO-Drug Dictionary, ICD-10) and appropriate software
7P2	Enter data from an ICSR into an electronic database using the ICH-E2B format and available software
7P3	Retrieve ICSRs from a database with various questions and at different levels of precision and aggregation, using available software
8P	**Signal detection and management: finding and analysing remarkable features of a set of ICSRs**
8P1	Analyse an ICSR series with respect to a potential signal of a specific new ADR using clinical judgement without statistics
8P2	Analyse an ICSR database for a signal of statistically significant reporting disproportionality of a new ADR by calculating the PRR using available software
8P3	Analyse an ICSR database for a signal of a new reporting trend, drug-drug interaction or a syndrome of several ADRs occurring more often together than would have been predicted from chance
9P	**Post-authorisation observational studies**
9P1	Appraise a real or fictitious report of a cohort or case-control study. Systematically identify weaknesses according to objective, population, endpoint, bias, confounding, power, statistical tests etc
9P2	Design a case-control study to investigate a suspected relevant difference in the frequencies of a rare serious ADR related to two drugs of the same class. Address risk factors and possible distortions
9P3	Design the set-up of a drug- or disease-related register to monitor ADRs in a given scenario. Address data collection, database structure, data fields, data validation and analysis, potential for record linkage, access and confidentiality
10P	**Benefit/risk assessment**
10P1	Appraise a published report 'Benefit/risk assessment of X'. Address the relevance and validity of risk and benefit measures, relation to the target disease, comparability, frequency of manifestation (relative, absolute)
10P2	Assess benefit/risk in a detailed scenario of a common non-serious illness treated by a herbal drug, the efficacy of which has never been shown in a randomised trial but which may cause rare serious ADRs
10P3	Assess benefit/risk in a scenario where a vaccine which causes rare, serious ADRs is clearly effective in preventing a potentially fatal disease, the incidence of which has, however, only been estimated
11P	**Pharmacovigilance and risk management systems, risk management plans, inspections**
11P1	Assess a real or fictitious RMP with flaws, provided in the context of a marketing authorisation application of a novel promising drug with conceivable but incompletely investigated risks. Define deficits
11P2	Assess a real or fictitious pharmacovigilance system document of a medium-size pharmaceutical company revealing specific deficits of the system. Find the deficits, propose amendments
11P3	Assume the role of a QPPV of a multinational company. You discover that in one country an unfavourable outcome of a phase IV study was concealed. Outline your action, including preparation for inspection

Table 3 continued

12P	**Industry and regulatory authorities, mandatory procedures from legislation**
12P1	Consider a range of different AE cases submitted to a multinational company from various sources in several countries. Describe, on the basis of current legislation, how the reports should be handled
12P2	Assess a real or fictitious PBRER with discrepancies between risk-relevant data (single fatality cases, line listing, studies) and the description of benefit/risk and necessary actions. Define deficits and flaws
12P3	Propose, based on detailed information about a newly discovered and confirmed ADR, its description in the SmPC and the patient information leaflet, including the appropriate paragraph(s), and the management of this variation
12P4	Develop an SOP to implement a specific PV procedure, e.g. assessment of an RMP
13P	**Pharmacovigilance organisation and public health**
13P1	Outline means to stimulate ADR reporting in a resource-limited setting: design a simple-to-handle reporting form with relevant fields and propose technical means to collect and transmit information
13P2	Outline principles and steps to set up a national PV centre in a low-income country. Address personnel, ICSR database and software, communication with patients and HCPs, SOPs
13P3	Design a CEM to monitor ADRs of an anti-infective drug used in the context of a public health programme in a resource-limited country. Discuss relevant elements of the study and methodological alternatives
13P4	Assess, on the basis of an existing performance indicator check list, a real or fictitious PV system
14P	**Communication**
14P1	Propose a response of the drug authority, in terms of public communication, to a TV report on three cases of a fatal ADR which was not yet confirmed in studies and is not described in the SmPC.
14P2	Propose, based on a detailed scenario of a drug-related problem and on relevant recommendations, a company Direct Healthcare Professional/Provider Communication.
14P3	Design a patient information leaflet for distribution by health professionals, based on a detailed scenario of a drug-related problem in a low-resource, multi-language country with prevalent illiteracy.
14P4	Draft a manuscript for publication of an ADR case or a case series in a scientific journal
15P	**Sources of information**
15P1	Outline the strategy of a systematic literature review considering a specific ADR of a class of drugs: journals, databases (e.g. PubMed, EMBASE), time window, type of publication
15P2	Put this into action: define a question; select keywords, inclusion and exclusion criteria, keyword combinations; adjust the search according to the actual number of hits and their usefulness
15P3	Conduct an online search for a specific information, e.g. a regulation, guideline, drug monograph, sales figure, disease prevalence, TV recording
15P4	Identify potential sources for funding and develop a grant proposal

ADR adverse drug reaction, *AE* adverse event, *AEFI* adverse event following immunisation, *CEM* cohort event monitoring, *DSUR* Development Safety Update Report, *ICD* International Classification of Diseases, *ICH* International Conference on Harmonization, ICH E2B guideline no. E2B of the ICH, *ICSR* Individual Case Safety Report, *MedDRA* Medical Dictionary for Regulatory Activities, *PBRER* periodic benefit- risk evaluation report, *PIL* Patient Information Leaflet, *PROSPER* Patient Reported Outcomes Safety Event Reporting Consortium, *PRR* proportional reporting ratio, *PV* pharmacovigilance, *QPPV* qualified person for pharmacovigilance, *RMP* Risk Management Plan, *SmPC* Summary of Product Characteristics, *SOP* standard operating procedure, *WHO-ART* WHO Adverse Reaction Terminology

Table 4 An example of how a subsection of the theoretical chapter 15, with keywords and examples, would look like in the 'IV levels of hierarchy' version of the curriculum

15.1.1 Databases with spontaneous ADR reports
UMC: 'VigiBase'. EMA: 'EudraVigilance'. Some national PV centres permitting access to anonymised ICSRs, e.g. US FDA, Health Canada, NL Lareb, DE BfArM/PEI. ADR databases of regional PV centres or hospitals for specific users. Problems to get reliable primary information in resource-limited settings

ADR adverse drug reaction, *EMA* European Medicines Agency, *ICSR* Individual Case Safety Report, *PV* pharmacovigilance, *UMC* Uppsala Monitoring Centre

that some people would prefer a different relative weighting of the chapters or sections on their respective level of hierarchy. Others may also criticise the rather homogenous and comprehensive character of the curriculum, arguing that only courses with contents tailored to the interest and need of the specific audience can be useful.

4.2 General Opportunities Offered by the Structure of the Curriculum, and Concrete Options for its Use

Considering these potential criticisms, we believe, however, that they may be counter-balanced by the broad-based and hierarchical structure of the curriculum. This structure allows almost every kind of focusing on specific issues and going into depth as needed, while maintaining the overall context. There are mainly three factors through which this flexibility is achieved:

1. The large number of theoretical modules on different levels of hierarchy and related practical tasks offers an opportunity for the organiser to tailor a course according to the already existing knowledge and experience, as well as the specific situation and need of the trainees and the available time.
2. The evenly developed structure of the theoretical part with chapters and sections of about equal length suggests its use in a way that similar periods of time can be allocated to individual units.
3. Likewise, the proposed 12 sets of practical tasks are designed in a way that it should be possible to formulate specific exercises which can be fulfilled within approximately equal periods of time.

The curriculum can be applied to an intensive course offered over several weeks where a whole day is devoted to each of the 15 theoretical chapters. In this case, the typical four-quarters of a day can easily be allocated to the four sections of every chapter. Also, one day each could additionally be allocated to the proposed 12 sets of exercises, or even to individual practical tasks. At the other end of the options, there may only be an opportunity to give a 1-day course and go over the majority of the contents of the theoretical chapters at a high level within the day, without further delving into the individual sections or even subsections, let alone any inclusion of hands-on training.

Also, there are various opportunities of tailoring a course specifically to the needs of the audience.

For example, the emphasis put on the 15 theoretical chapters and their sections on the one hand, and on the training of practical skills on the other, should be chosen according to the specific training situation. This could be planned in advance or decided upon in specific situations during the actual conduct of a course where a trainer may wish to include some hands-on exercises. These could be expected to enhance active audience participation and to facilitate dialogue and interaction among her- or himself and the course participants.

Using the curriculum for a 'zooming' course may be considered on occasion. This would put a specific narrow topic in perspective, i.e. its place within the field of PV. In this case, one would first devote some time for a broad overview of the whole scope of PV on the chapter level, thereafter address a specific chapter with its four sections, and finally focus on one specific section with its set of subsections or even just on a specific subsection, possibly intensified by one or several of the practical tasks.

A further option would be some kind of 'cluster teaching', i.e. training in related chapters such as 'individual case safety reports' plus 'spontaneous reporting systems', 'signal detection' plus 'post-authorisation observational studies' or 'communication' plus 'sources of information'. Other aspects may specifically apply to the local situation, recent drug regulations, a current safety problem or individual ADR cases reported in the media. These topics might not be part of a standard international curriculum but might be useful supplements as lively illustrations and stimuli for discussion on a case-by-case basis.

4.3 The Way Forward

For some of the theoretical chapters we have started to develop sets of keywords and examples relating to each of the subsections in order to further detail and illustrate their meaning. Such an additional breakdown of the subsections might be considered as the creation of a further level of hierarchy ('level IV'). Our aim is to complete this work for all 15 chapters. Also, we may add more proposals for practical tasks to choose from. However, such a detailed curriculum would probably be too extensive for publishing in a printed international journal. It is planned, therefore, to make this version available electronically in *Drug Safety* or on the homepages of WHO and ISoP. An electronic version could be updated relatively easy and as often as necessary in a modular fashion, in line with how PV in scientific, public health and regulatory terms will evolve in the future. Also, online availability would facilitate the use of the curriculum for long-distance courses. An example of a subsection with keywords drawn from an already detailed theoretical chapter is shown in Table 4 to illustrate how it is envisaged the curriculum would look like at the 'fourth level of hierarchy'.

For any revision of this curriculum in the future and also for the development of the detailed 'level IV' version, we would be grateful for comments and suggestions and for feedback from applying the curriculum, as we hope that it will be used by many organisations and trainers and prove helpful for professional capacity building.

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