There is an urgent need to develop robust pharmacovigilance systems for antiretrovirals particularly in resource-limited settings. This detailed manual gives a step by step approach to undertaking the pharmacovigilance of these medicines. Good pharmacovigilance will identify the risks in the shortest possible time after the medicine has been marketed and will help to identify risk factors. This manual describes the principles of both spontaneous reporting systems and cohort event monitoring programmes. It is intended to be a source of practical advice for Pharmacovigilance Centres and health professionals involved in HIV/AIDS programmes.

Following the success of the manual, which was first published in 2009, this new edition includes revised questionnaires and guidance documents, making it an even more valuable resource for all who are involved in the development of pharmacovigilance systems for antiretrovirals.

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A PRACTICAL HANDBOOK ON THE PHARMACOVIGILANCE OF ANTIRETROVIRAL MEDICINES

WHO

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World Health Organization

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Abbreviations

ADRs	adverse reactions to medicines (adverse drug reactions)
ART	antiretroviral therapy
ARV	antiretroviral
ATC	Anatomic Therapeutic Chemical (Classification for medicines)
BCPNN	Bayesian Confidence Propagating Neural Network
CEM	cohort event monitoring
CemFlow	Cohort Event Monitoring data entry and analytical tool
DD	(WHO) Drug dictionary
ICD 10	WHO International classification of diseases version 10
IMAI	integrated management of adolescent and adult illness
ICSR	individual case safety report(s)
MedDRA	Medical dictionary for drug regulatory activities
OI	opportunistic infection
IMMP	(The New Zealand) Intensive Medicines Monitoring Programme
PEM	prescription event monitoring
PvC	Pharmacovigilance Centre
SOC	system organ class
SOP	standard operating procedure
UMC	the Uppsala Monitoring Centre
VigiBase	WHO database of individual case safety (ADR) reports (ICSR)
VigiFlow	spontaneous reporting data entry and analytical tool

VigiMine	data mining tool available as part of VigiSearch
VigiSearch	search tool for searching the VigiBase database
WHO	World Health Organization
WHO-ART	WHO adverse reactions terminology

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A. Introduction

This is a detailed manual giving a step by step approach to undertaking the pharmacovigilance of antiretrovirals. It is intended to be a source of practical advice for Pharmacovigilance Centres and health professionals involved in HIV/AIDS prevention and treatment programmes. A number of WHO publications are available that provide a background to pharmacovigilance and, as far as possible, that material will not be repeated here. Health officials, planners, the staff of Pharmacovigilance Centres, public health teams and all health workers should become familiar with these publications, which are:

- *Safety of Medicines: A guide to detecting and reporting adverse drug reactions*
- *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*
- *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre*
- *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool*
- *Patient monitoring guidelines for HIV care and ART*
- *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*
- *Chronic HIV care with ARV therapy and prevention*

These booklets are available free from Quality Assurance and Safety of Medicines, WHO, Geneva, Switzerland (qsm@who.int).

1. Pharmacovigilance

1.1 Definition

Pharmacovigilance has been defined as: *The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem* (WHO).

1.2 Explanation

Pharmacovigilance is an arm of patient care. It aims at getting the best outcome of treatment with medicines. No one wants to harm patients, but unfortunately, because of many different factors, any medicine will sometimes do this. Good pharmacovigilance will identify the risks in the shortest possible time after the medicine has been marketed and will help to establish and/or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with potential for preventing many adverse reactions and will ultimately help each patient to receive optimum therapy at a lower cost to the health system.

The organizers of a monitoring programme for the safety of medicines used to treat HIV infection must have a clear sense of the questions they want to answer before developing their plan. It is only with clear goals in mind that one can design a proper data collection instrument and an analytical plan.

The following sections list the potential outcomes of monitoring which can be prioritized for goal-setting and selecting the most appropriate method(s) of safety surveillance in the programme.

1.3 General aims

The general objectives of this handbook are to:

1.3.1 improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;

1.3.2 enhance public health programmes by collecting good information on the effects of medicines and develop early warning of problems which might affect the success of the programme;

1.3.3 improve public health and safety in relation to the use of medicines;

1.3.4 detect problems related to the use of medicines and communicate the findings in a timely manner;

1.3.5 contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;

1.3.6 encourage the safe, rational and more effective (including cost-effective) use of medicines;

1.3.7 promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

1.4 Specific aims

The specific aims of this Handbook are to enable:

1.4.1 the identification of signals of serious adverse drug reactions (ADRs) following the introduction of a new drug or drug combination;

1.4.2 the assessment of signals to evaluate causality, clinical relevance, frequency and distribution of ADRs in particular population groups;

1.4.3 the rapid identification of events that are likely to affect adherence to treatment and determination of their rates and the risk factors that make these events more likely with the aim of reducing their occurrence;

1.4.4 the calculation and evaluation of rates of events so that:

- 1.4.4.1 risk can be measured;
- 1.4.4.2 the safety of medicines can be compared and informed choices made;
- 1.4.4.3 risk factors can be clearly identified;

1.4.5 the communications with and recommendations to authorities and the public;

1.4.6 the appropriate response or action in terms of drug registration, drug use and/or training and education for health professionals and the public;

1.4.7 the measurement and evaluation of outcome of response or of action taken (e.g. reduction in risk, improved drug use, or improved outcome for patients experiencing a particular adverse reaction);

1.4.8 the appropriate feedback to the clinicians who provided the information.

1.5 Pharmacovigilance of antiretrovirals

There is considerable experience in the developed world with the use of antiretroviral medicines (ARVs). These medicines are associated with significant safety concerns including serious ADRs, with both short- and long-term effects. The outcome of these long-term adverse effects is unknown. The major events linked to the use of antiretroviral medicines include altered body fat distribution (lipodystrophy), anaemia and neutropaenia, hypersensitivity reactions, hepatic disorders, acute pancreatitis, altered bone structure (osteopaenia and osteoporosis), muscle damage (myopathy) of the newborn and lactic acidosis. These may damage confidence in any national ARV programme and affect patient adherence. With the erosion of confidence in the

safety of medicines and of the programme, patients may stop taking these life-prolonging medicines leading to problems for themselves and for society as a whole. Poor adherence is known to lead to failure of therapy in the patient and in addition, to increase the possibility of development of drug-resistant viral strains leading to reduced efficacy.

Little is known about the toxicity profile of ARVs in developing countries. These countries have special factors and conditions that are very different from those of the developed world and medicine use and its safety may therefore vary considerably. The relevant factors and conditions include the existence of comorbid conditions such as a high prevalence of tuberculosis (TB), malaria and other infections of all types; malnutrition; reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; irrational use of prescription medicines; and likelihood of medicine interactions. In addition, some local systems for the delivery of health care may rely on people who have limited training, knowledge or expertise, and medicine regulatory systems that are either rudimentary or nonexistent and are not adequately equipped to deal with medicine safety issues.

The monitoring of ARVs in these populations is therefore of paramount importance, and methods of monitoring are the subject of this handbook.

2. Pharmacovigilance centre

The Pharmacovigilance Centre (PvC) of an individual country is responsible for meeting the requirements for pharmacovigilance of all medicines and is a centre of expertise for the art and science of monitoring and analysis, and use of the analysed information for the benefit of patients. National and any regional Pharmacovigilance Centres should be set up with the approval of the authority responsible for the regulation of medicines ("regulatory authority"). The centre may function within the regulatory authority, a hospital, an academic institution or as an independent facility such as a trust or foundation.

In the absence of a PvC, the HIV/AIDS programme should include in its budget, funding for catalysing and facilitating the establishment of a PvC, or for improving resources if an established PvC is incapable of coping with the demands of the pharmacovigilance of ARVs. This would be a legitimate and wise call on the funds of the programme because pharmacovigilance should result in better therapeutic management, more acceptable and safer treatment. Countries applying for grants to support ARV treatment should include pharmacovigilance of ARVs as a core component of their prevention and treatment programmes.

B. Passive or active pharmacovigilance?

1. Passive pharmacovigilance

Passive surveillance means that no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. This is the most common form of pharmacovigilance. It is commonly referred to as "spontaneous" or "voluntary" reporting. In some countries this form of reporting is mandatory. Clinicians, pharmacists and community members should be trained on how, when and what to report.

2. Active pharmacovigilance

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. This surveillance is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as **hot pursuit**. The most comprehensive method is cohort event monitoring (CEM). Cohort event monitoring is often referred to as prescription event monitoring (PEM), but this terminology is inappropriate where individual prescriptions with subsequent dispensing are not part of the process of provision of medicines. Examples of CEM are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and Prescription Event Monitoring (PEM) in England. A similar method is being used successfully in China to monitor contraceptives and includes monitoring in rural areas. CEM is an adaptable and powerful method of getting good comprehensive data.

Other methods of active monitoring include the use of registers, record linkage and screening of laboratory results in medical laboratories.

Methods for both passive (spontaneous reporting) and active pharmacovigilance (CEM) will be described. The essential and interesting tasks of causality assessment and signal identification are applicable to both methods of surveillance and will be covered in detail after the individual methods have been discussed.

C. Spontaneous reporting

1. Introduction

1.1 Background

1.1.1 Definition of a spontaneous report

A spontaneous report is an unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

1.1.2 Throughout the world spontaneous reporting is the most common method of surveillance. It is the easiest to establish and the cheapest to run, but reporting rates are generally very low and subject to strong biases and there is no database of all users or information on overall drug utilization. These problems prevent the accurate assessment of risk, risk factors or comparisons between drugs. Nevertheless spontaneous reporting has played a major role in the identification of safety signals throughout the marketed lifetime of medicines in general.

1.2 Adverse reactions

1.2.1 It should be noted that this method is for the reporting of suspected *adverse reactions* (and not events in general).

1.2.2 The definition of an adverse reaction is: a *response to a medicine which is noxious and unintended, and which occurs at doses normally used in man* (WHO).

2. Objectives

2.1 The purpose of spontaneous reporting

Pharmacovigilance using a spontaneous reporting system is designed to detect ADRs not previously observed in preclinical or clinical studies, to improve understanding of the potential risks, including reactions resulting from drug interactions or drug effects in particular populations, and to help provide a basis for effective drug regulation, education and consequent changes in practices by prescribers and consumers.

2.2 Background to the methodology

2.2.1 *A spontaneous report is an unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme*. A new term has been introduced that will supplant the use of 'spontaneous reports'. This is 'individual case safety reports (ICSR)'. This term will be used in this handbook.

2.2.2 ICSRs play a major role in the identification of signals of risk once a medicine is marketed. ICSRs can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

2.2.3 Spontaneous reporting is dependent on clinicians and other health professionals who need to be trained and encouraged to report details of suspected adverse reactions in patients on ARV treatment. Under-reporting is a serious problem with this method, but reporting can be intensified in selected units e.g. hospitals.

2.2.4 There is no standard global reporting form for ICSRs as the needs of countries differ and it is important that they are involved in developing their own form. If a national pharmacovigilance system is in place, then it is preferable to use the reporting form already in use. A variety of options for reporting should be considered: the formal reporting cards can be collected on a regular basis; mailed individually or in bulk; faxed; sent electronically by e-mail or on the Internet if the forms are made available in electronic format. Reports can also be made by telephone. Ease of reporting is a key factor in achieving a good rate of reporting.

2.2.5 Health professionals will need advice on what types of suspected adverse reactions to report. Most pharmacovigilance programmes request reports of all serious events which include death and congenital abnormalities (the international definition of seriousness is given in section 2.3.2 below), and in addition, all suspected reactions to new medicines. In general, deaths are very poorly reported. The particular requirements for ARV monitoring would need to be specified e.g. reactions that affect adherence, reactions of special interest, and all suspected reactions in children and pregnant women.

2.2.6 All ICSRs should first be sent to the pharmacovigilance centre in the country for evaluation. The processing of data will be the same as for cohort event monitoring. Spontaneous reporting for ARVs should be integrated with the national pharmacovigilance programme and regarded as an ongoing monitoring method to be continued after any special studies are completed.

2.2.7 The reports should then be forwarded by the PvC to the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre (UMC)) for entry into a global database that uses systematic methods for the detection of safety signals from ICSRs. These methods include the use of Bayesian Confidence Propagating Neural Network (BCPNN) and other techniques for signal detection. Data-mining techniques should always be used in conjunction with, and not in place of, analyses of single case-reports. Data-mining techniques facilitate the evaluation of ICSRs by using statistical methods to detect potential signals for further evaluation. Confounding factors that influence reporting of ICSRs are not removed by data-mining. The results of data-mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate for different medicines, at different times and in different countries and the many other potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

2.3 Serious reactions

2.3.1 Much importance is placed on the reporting of serious reactions.

2.3.2 A serious adverse reaction is: any *untoward medical occurrence that at any dose results in death, is life threatening, requires or prolongs patient hospitalisation, results in persistent disability/incapacity, or is a congenital anomaly/birth defect* (International Conference on Harmonisation (ICH)).

2.3.3 The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

2.3.4 Medical and scientific judgement should be exercised in deciding whether other situations are serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias, convulsions not resulting in hospitalization or development of drug dependency or drug abuse.

3. Minimum reporting requirements

3.1 WHO criteria

According to WHO criteria, the following basic information is required before a report is acceptable:

3.1.1 an identifiable source of information or reporter;

3.1.2 an identifiable patient;

3.1.3 name(s) of the suspected product(s);

3.1.4 a description of the suspected reaction(s).

3.2 Other practical conditions

3.2.1 The system depends on written records using a standard reporting form. For this reason the reporter must be literate and the reporting system extends only to the clinic and dispensary level of the health care system.

3.2.2 Informal health care providers, because of their varying degrees of literacy, cannot act as reporters, but should play an important role in referring patients to health facilities where reports can be made.

4. How to report

4.1 Reporting form

Over 100 different reporting forms are available. These have been developed individually by each country that has set up a PvC. To be effective a reporting form needs to be available in the local language(s) and have features relating it to the responsible authority e.g. a logo, and the address and contact details of the issuing institution. The form from Ghana (Annex 1) for use in monitoring ARVs is a good example.

4.1.1 PvCs will have, or should develop their own national reporting forms.

4.1.2 Forms should be simple and easy to complete.

4.1.3 They should not request too much information, particularly information that is difficult to find and record, or information that is unlikely to be used.

4.1.4 There should be sufficient space in which to describe the suspected reaction(s).

4.1.5 They should be widely distributed to all health professionals including those who are treating HIV/AIDS and those who are working privately. Difficulty in finding a reporting form is a common barrier to reporting.

4.1.6 The forms should be printed on a single page and easily folded and sealed.

4.1.7 To facilitate postage, the return address should be printed on the outside, with postage pre-paid.

4.1.8 It is desirable to have only one type of reporting form available in the country for use for all medicines including ARVs.

4.2 Other options for reporting

Reporting needs to be made as convenient as possible. If other methods are available, they may be preferred by some health professionals, but full confidentiality needs to be respected. Preferences may vary between clinics and hospitals, private or government facilities and public health programmes. Suitable methods might include:

4.2.1 *Telephone*. The person receiving the report should have a reporting form to record the details and make sure that essential data is not missing.

4.2.2 *Fax*. Sending reports by fax is equivalent to posting the report, but faster. A fax machine is a very important asset for a national PvC and its major sentinel sites.

4.2.3 *E-mail*. A written case-report submitted by e-mail may be acceptable. Further details can be obtained by follow-up. Reporting forms can be sent to reporters as e-mail attachments and they can be e-mailed, faxed or posted to the PvC when completed.

4.2.4 *The Internet*. An Internet site is a valuable asset for a PvC and a reporting form could be made available for downloading or for completion online (entering data through web-based data entry) if the site is secure.

5. Where to report

5.1 Reports should be sent to the PvC.

5.2 If it is not practical to send the forms directly to the centre, it may be necessary to arrange points of collection at other sites such as specific hospitals or clinics.

5.3 The reports should be stored securely to maintain privacy.

6. What to report

6.1 Essential data elements

6.1.1 Patient details

6.1.1.1 Health number: this may be a national identifier (preferred), hospital, clinic, or programme number.

6.1.1.2 Name: full name as an accurate identifier for follow-up purposes and avoidance of duplication.

6.1.1.3 Address: to allow for follow-up and accurate identification. This may take various forms depending on the location.

6.1.1.4 Sex.

6.1.1.5 Date of birth (preferred) or age (add 'est' if age is estimated).

6.1.1.6 Weight and height.

6.1.2 Patient medical history of significance – examples

6.1.2.1 Renal disease.

6.1.2.2 Liver disease.

6.1.2.3 Malnutrition.

6.1.2.4 Tuberculosis.

6.1.3 Details of medicines

6.1.3.1 Name(s): (this may be brand or generic) and formulation (e.g. tablets, syrup, injection). Reporting the brand name gives more specific information. The use of standard abbreviations for ARV medicines or regimens would simplify recording. Recommendations on how best to record ARV therapy would need to be part of a standard operating procedure (SOP) for completion of the reports.

6.1.3.2 Mode of administration (e.g. oral, rectal, injection).

6.1.3.3 Indication(s) for use.

6.1.3.4 Dose: for most medicines with fixed dosing, recording the total daily dose is appropriate. For ARVs, recommendations for recording dose should be part of an SOP and could be referred to by regimen for the appropriate age group. It is important to simplify recording as much as possible without sacrificing accuracy.

6.1.3.5 Date of commencement.

6.1.3.6 Date of withdrawal.

6.1.3.7 Duration of use, if dates of commencement and withdrawal are not available.

6.1.3.8 All medicines being taken at the time of the event should be listed. Each suspect medicine can be indicated by an asterisk.

6.1.4 Reaction details

6.1.4.1 Date of onset.

6.1.4.2 Reporters should be asked to give a brief clinical description. They should not be asked to give the official pharmacovigilance reaction term.

6.1.4.3 Laboratory test results if available, together with units.

6.1.4.4 Outcome of event: resolved, resolving, no change, disabling, worsening, death (with date), congenital anomaly.[1]

6.1.4.5 Effect of rechallenge (if any).[2]

6.1.5 Reporter details

6.1.5.1 Name.

6.1.5.2 Contact details.

6.1.5.3 Status: e.g. physician, nurse, patient.

6.1.6 Date and place of report

6.2 Advice to reporters

6.2.1 Suggest that they report any adverse event of concern.

6.2.2 Report all suspected serious reactions. A serious reaction:

6.2.2.1 results in death;

6.2.2.2 is life-threatening;

6.2.2.3 requires hospitalization or prolongation of hospitalization;

6.2.2.4 results in persistent disability;

6.2.2.5 is a congenital anomaly.

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[1] These terms are standard E2B terms, which should be adhered to.

[2] Rechallenge is the voluntary or inadvertent re-administration of a medicine suspected of causing an adverse reaction.

6.2.3 Report persistent adverse reactions that could threaten adherence.

6.2.4 Advise reporters that they do not need to be sure that the medicine caused the event.

6.3 Follow-up when necessary

6.3.1 All reports of serious events should be followed up if details are incomplete. This may require the involvement of health professionals trained and appointed for this type of work.

6.3.2 Occasionally follow-up information is required to fully assess reports of non-serious events. Follow-up requests should be kept to a minimum because they can act as a deterrent to further reporting. Examples might be:

6.3.2.1 a request for essential missing details;

6.3.2.2 information on the final outcome;

6.3.2.3 the result of rechallenge;

6.3.2.4 the results of laboratory tests;

6.3.2.5 postmortem results from the health facility where autopsy is undertaken.

7. When to report

7.1 A report should be completed as soon as possible after the reaction.

7.2 It is better to advise reporters not to wait until final results and information such as hospital letters are received, because the report may be forgotten. These additional details can be sent to the PvC later.

8. Who should report

The following is a list of potential reporters. They may work in the public or private health sectors.

8.1 Physicians.

8.2 Pharmacists.

8.3 Nurses.

8.4 Other (literate) health and community workers should be encouraged to detect and report, preferably to the clinician who prescribed the treatment, or directly to the PvC.

8.5 Public health programmes.

8.6 Pharmaceutical companies.

8.7 Patients or patient representatives.

9. Sharing the results

9.1 Individual, immediate

9.1.1 Anyone who sends in a report should receive a letter of thanks and further reporting forms.

9.1.2 In addition, the letter should provide some brief information about the reaction reported, such as, but not normally including all, of the following:

- 9.1.2.1 number of reports of the reaction in the centre's database;
- 9.1.2.2 number of reports of the reaction in the WHO database;
- 9.1.2.3 information from the literature;
- 9.1.2.4 the importance of the reaction in the management of HIV/AIDS cases;
- 9.1.2.5 the safety or risk of further administration to the patient;
- 9.1.2.6 the possibility of preventing the reaction in other patients by indicating potential risk factors.

9.2 Relevant summaries or reviews

9.2.1 From time to time, the Centre should prepare a summary of the reactions reported and/or safety reviews of the ARVs being used.

9.2.2 These should be distributed widely as bulletins or newsletters, including to national programme managers.

9.2.3 News items should be prepared for the local media on overall effectiveness and safety, or about particular issues that have arisen.

9.3 Regular transmission to the WHO database

Details of reports should be sent for international analysis to the WHO Collaborating Centre for International Drug Monitoring (UMC). The use of VigiFlow (described below) simplifies this procedure.

10. Data entry

10.1 Options

There are few, if any, commercial software products available to suit the needs of PvCs for data entry, storage and analysis. The UMC can provide access to VigiFlow which is a tool designed for these functions. It is the best option available.

10.2 VigiFlow

10.2.1 It is web-based and requires no local support or maintenance.

10.2.2 VigiFlow provides an online database for the use of the PvC. Data entered are confidential to, and are owned by the country that enters them. The PvC decides what data can be transferred to the international WHO database (VigiBase) and when it will be transferred.

10.2.3 VigiFlow provides for standardized entry of data from reports.

10.2.4 It has built-in error avoidance features.

10.2.5 It provides access to a search and statistics database online.

10.2.6 National data can be accessed and used by the local PvC.

10.2.7 Standardized outputs are available for:

- 10.2.7.1 summary tabulations;
- 10.2.7.2 a range of standard statistical analyses.

10.2.8 The data can be exported to a local country database (e.g. Excel) for ad hoc searches and to meet local analytical requirements.

10.2.9 It provides live access to up-to-date terminologies:

- 10.2.9.1 WHO Drug Dictionary (DD) and MedDRA;
- 10.2.9.2 WHO Adverse Reactions Terminology (WHO-ART).

10.2.10 The completed reaction reports can be easily exported to the WHO database (VigiBase).

D. Cohort event monitoring

1. Introduction

1.1 Event monitoring

1.1.1 Definition

1.1.1.1 An adverse event (sometimes called an adverse experience) is defined as, "*Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment*."

1.1.1.2 Explanation
An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgement on its causality. (Favourable events may be recorded as an indication of an unexpected therapeutic effect.)

1.1.1.3 Cohort event monitoring (CEM) records all clinical events and not just suspected adverse reactions.

1.1.2 Event monitoring involves:

1.1.2.1 actively asking for reports of the events;

1.1.2.2 systematically asking for reports of the events.

1.2 Description

1.2.1 Cohort event monitoring (CEM) is a prospective, observational, cohort study of adverse events associated with one or more medicines.

1.2.2 This methodology is often referred to as prescription event monitoring (PEM), but this terminology is inappropriate when individual prescription with subsequent dispensing by pharmacists is not part of the process of supplying medicines to patients. In most developing countries, the treatment of HIV is not provided on a prescription basis. Examples of CEM methodology are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and PEM run by the Drug Safety Research Unit in England.

1.2.3 A CEM programme is essentially an observational study, in normal clinical practice, of a new medicine in the early postmarketing phase, but it can be used for older medicines. (see PEM in Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007).

1.2.4 Its basic function is to act as an *early warning system* of problems with new medicines, although it will provide much more.

1.3 Objectives

1.3.1 The objectives of spontaneous reporting (see section C.2) are also objectives of CEM. The aims of CEM include the following, either in addition to, or more effectively than for spontaneous reporting.

1.3.2 Provide incidence rates for adverse events as a measure of risk.

1.3.3 Characterize known adverse reactions.

1.3.4 Detect signals of unrecognized reactions.

1.3.5 Detect interactions with other medicines, complementary and alternative medicines, foods and concomitant diseases.

1.3.6 Identify risk factors and thus provide evidence on which to base effective risk management.

1.3.7 Assess safety in pregnancy and lactation.

1.3.8 Provide a measure of comparative risks between medicines.

1.3.9 Provide cohorts for further study of safety issues if required in the future.

1.3.10 Detect inefficacy, which might be due to:

- 1.3.10.1 faulty administration;
- 1.3.10.2 poor storage conditions;
- 1.3.10.3 poor quality product;
- 1.3.10.4 counterfeit product;
- 1.3.10.5 interactions.

1.4 Selection of drugs to monitor

1.4.1 It is intended that each of the different ARV regimens (combination ARV therapies) in use for the prevention and treatment of HIV will be monitored as a single treatment entity. Appropriate analyses at a later date will signal or determine the relationship between specific drugs–event combinations.

1.4.2 A drug substitution in any regimen creates a new treatment entity.

1.5 Basic processes

1.5.1 Establishing a cohort of patients for each drug and/or drug regimen.

1.5.2 Recording adverse events experienced by patients in the cohort(s).

1.6 Programme duration

1.6.1 For most medicines other than ARVs the duration of monitoring is limited. It should be considered in terms of:

1.6.1.1 the duration of treatment to be monitored in individual patients; and

1.6.1.2 the duration of the programme as a whole, which is determined (in part) by reaching the desired cohort size.

1.6.2 For short-term therapy (e.g. for malaria), these two considerations are decided, respectively, according to:

1.6.2.1 the length of treatment required for the illness, plus an additional period in which delayed reactions might become evident (e.g. one month);

1.6.2.2 the length of time required to recruit the target population for the cohort. Each patient must be monitored from the commencement of treatment and new patients are added to the cohort as their treatment begins.

1.6.3 For long-term therapy:

1.6.3.1 treatment for individual patients is monitored for a period that is considered to be appropriate for the identification of both short-term and long-term term effects (e.g. for an antihypertensive this might be 4 years);

1.6.3.2 the programme will continue until the target cohort population is reached (e.g. 10 000).

1.6.4 For ARV therapy:

1.6.4.1 treatment for individual patients is life-long;

1.6.4.2 serious toxicities can develop after prolonged exposure to ART in terms of years;

1.6.4.3 it is important to understand the natural history of serious toxicities;

1.6.4.4 monitoring will therefore need to be prolonged, at least for particular subgroups of the cohort.

1.6.2 If there is particular interest in certain subgroups e.g. pregnant women or children or those who experience an event of concern, then monitoring may need to continue for a longer period to get sufficient numbers to evaluate these subgroups at a satisfactory level of statistical significance.

1.6.3 A practical approach is to review the data at regular intervals (e.g. 3-monthly). Trends may then be observed that indicate the need for an extension of monitoring.

2. Epidemiology

The key epidemiological characteristics of CEM can be described as:

2.1 Observational

This means that the studies are "*non-interventional*" and are undertaken in real-life situations. Patients are not selected according to any criteria: all patients who receive ART are included until the desired cohort size is achieved. This includes patients of all ages, those with other diseases and those on other medicines. Treatment is given according to the usual local guidelines.

2.2 Prospective

This means that CEM is planned before the patients are treated and ART is monitored until the end of the programme, or until they cease to receive treatment for whatever reason.

2.3 Inceptional

This has a similar meaning to prospective: that every patient is followed-up for adverse events from the time of commencement of their treatment.

2.4 Dynamic

This means that new patients are added as the study continues until such time as there are sufficient numbers in the cohort.

2.5 Longitudinal

This means that the occurrence of any events in patients are observed over a period of time until the end of the programme, or until they cease to receive treatment with the monitored medicines.

2.6 Descriptive

This means that all events are identified and described, their frequency is measured and their distribution in different subgroups of interest in the cohort is recorded and analysed.

3. First step – implementation

The implementation step has to be performed well if a CEM study is to succeed.

To ensure this it is necessary to do the following:

3.1 First action

Appoint a full-time CEM coordinator.

3.2 Pilot exercise

Aim at running an initial pilot programme.

3.3 Sites and training

Select appropriate sentinel sites, with trained teams and adequate resources to perform CEM.

3.4 Advocacy

See notes on communication in section N and Annex 14.

Using the most appropriate means, all stakeholders must be fully informed of the:

3.4.1 reasons for monitoring (see next section: D3.5);

3.4.2 methodology as it involves them;

3.4.3 value of safety monitoring and the advantages of CEM;

3.4.4 contribution it will make to the health of the population (improving benefit and reducing risk);

3.4.5 potential for increasing the effectiveness of public health programmes;

3.4.6 potential for reducing health costs for the community and government;

3.4.7 contribution CEM programmes can make to the knowledge of ARV medicines and their safety in any particular country and internationally.

3.5 Reasons for monitoring

The following objectives need to be emphasized as the motivation for providing the data requested. They are similar to the objectives in D1.3, but have a promotional and advocacy emphasis rather than a descriptive one.

3.5.1 The earliest possible recognition of new adverse reactions, including interactions.

3.5.2 To measure risk (incidence), including comparative risk of different ART regimens or individual medicines.

3.5.3 To identify risk factors for the important reactions so that appropriate risk management can be applied and the risk of harm minimized.

3.5.4 To assess safety in pregnancy and lactation.

3.5.5 To provide evidence for:

- 3.5.5.1 effective risk prevention and management;
- 3.5.5.2 safer use of ARVs;
- 3.5.5.3 benefit or harm assessment of different regimens or products;
- 3.5.5.4 evidence-based regulatory action.

3.5.6 To provide cohorts for the future investigation of safety concerns that have arisen from monitoring or reports in the literature.

3.6 Approaches to advocacy

These need to be adapted for the target audience.

3.6.1 Personal meetings with people of influence in government and the ministry of health, regulatory authorities, academic institutions, hospitals, public health programmes, WHO offices, professional associations, the pharmaceutical industry, the privacy commissioner, the community and the media.

3.6.2 Give presentations at meetings of professional groups e.g. hospital doctors, nurses and pharmacists. This is best achieved at one of their regular meetings.

3.6.3 Produce and distribute leaflets for health professionals and patients.

3.6.4 Produce posters for patients and the community and distribute them to hospitals and clinics.

3.6.5 Cultivate good relationships with key media journalists on newspapers, magazines, radio and television and discuss your work as a newsworthy activity and to create a culture of medicines safety in civil society.

3.6.6 Encourage a feeling of collegiality and collaboration among health professionals in the interests of the health of the community, rather than taking an authoritarian approach.

3.6.7 Develop the detailed application of CEM methodology in consultation with the health workers in the hospitals and clinics.

4. Second step — establishing the cohort(s)

4.1 Numbers of patients

4.1.1 Factors to consider

4.1.1.1 See section D1.6.

4.1.1.2 With CEM in general, a cohort of 10 000 patients is usually recommended. This gives a 95% chance of identifying a specific event that has an incidence of 1:3000 (uncommon or rare). Normally several events are needed to alert to a signal, or help evaluate a problem.

4.1.1.3 A cohort of 3000 patients gives a 95% chance of identifying a single event with an incidence of 1:1000.

4.1.1.4 If a comparator study is being undertaken, greater numbers will be needed if the background incidence in the community is high (as with diarrhoea) and it is desired to detect statistically significant differences between the comparators.

4.1.1.5 Concomitant medicines: larger numbers might be needed to detect differences between patients on specific medicines (e.g. anti-tuberculous) and the other patients.

4.1.1.6 Other health problems e.g. malnutrition: larger numbers might be needed to detect differences in these patients.

4.1.1.7 Table 1 is useful for deciding on numbers, or estimating the statistical probability of a result with a particular number of patients.

4.1.2 Desirable cohort size

Taking the above factors into consideration, and because of the complexity of the issues surrounding the clinical care of patients with HIV, it would seem desirable to aim for a cohort of 15 000–20 000.

TABLE 1

Relationship between sample size and probability of observing an adverse event (AE). Per cent probability of observing at least one AE in the sample by AE expected incidence

	Expected AE incidence: 1 event out of … patients						
Sample size	**100**	**200**	**500**	**1 000**	**2 000**	**5000**	**10000**
200	86.47	63.21	32.97	18.13	9.52	3.92	1.98
300	95.02	77.69	45.12	25.92	13.93	5.82	2.96
500	99.33	91.79	63.21	39.35	22.12	9.52	4.88
700	99.91	96.98	75.34	50.34	29.53	13.06	6.76
1 000	100.00	99.33	86.47	63.21	39.35	18.13	9.52
1 500	100.00	99.94	95.02	77.69	52.76	25.92	13.93
2 000	100.00	100.00	98.17	86.47	63.21	32.97	18.13
3 000	100.00	100.00	99.75	**95.02**	77.69	45.12	25.92
5 000	100.00	100.00	100.00	99.33	91.79	63.21	39.35
7 000	100.00	100.00	100.00	99.91	96.98	75.34	50.34
10 000	100.00	100.00	100.00	100.00	99.33	86.47	63.21
12 000	100.00	100.00	100.00	100.00	99.75	90.93	69.88
15 000	100.00	100.00	100.00	100.00	99.94	95.02	77.69
20 000	100.00	100.00	100.00	100.00	100.00	98.17	86.47
20 000[a]	100.00	100.00	100.00	100.00	99.72	76.19	32.33

[a] Per cent probability of observing at least 3 AEs in the sample by AE expected incidence.

Note: The per cent probabilities to observe at least 1 AE and 3 AEs were calculated using binomial distribution.

As can be seen from Table 1, a sample size of 3000 patients gives a 95% probability of identifying a particular adverse event occurring at a rate of 1:1000, but for a meaningful assessment, at least three events usually need to be identified: hence the higher objective of obtaining a sample of 10 000 patients. However, the identification of one serious event can be clinically significant.

In relation to the comparison of two medicines (or regimens), two more tables and a graph are presented in Annex 2 as a guide to the cohort numbers required to reach sufficient statistical power to identify significant differences in the incidence of particular events. The minimum acceptable statistical power is 80%.

- Table 1 (above) shows the sample size required to identify statistically significant differences when the incidence is 0.1% (1:1000) in one of the comparators.
- Annex 2 (table A2.1 and A2.2) shows the power that can be achieved with different cohort sizes when the incidence of the event of interest in one of the comparators is 1%.
- Annex 2 (Figure 1):the graph illustrates the power that can be achieved at various levels of difference (RR) for comparison of an event in two medicines with cohort sizes of 1500.

4.2 Selection of patients

4.2.1 Logistics

4.2.1.1 Decisions will need to be made as to where the patients will be recruited and where the monitoring will be performed:

- the patients might be recruited from all health facilities involved in treatment of HIV infections;
- patients might be recruited from selected health facilities that are representative of the whole country, designated as "*sentinel monitoring sites*";
- from a practical point of view, sentinel sites may be selected where there is good infrastructure, good facilities and record keeping.

4.2.2 Inceptional

Patients must be monitored from the start of treatment (see section D2.3). Patients not seen at the beginning of their treatment should be excluded from the study.

4.2.3 Subgroups of interest

4.2.2.1 Children: In order to determine any risks or risk factors specific to children, the whole population of users will need to be monitored to enable comparison of children with the adults in the cohort.

4.2.2.2 Tuberculosis or other specific comorbidity: In order to determine any risk factors specific to patients with tuberculosis or another specific comorbidity, the whole population of users will need to be monitored to enable comparison with the cohort members who do not have tuberculosis or another disease of interest.

4.2.2.3 Pregnancy: If the only interest in monitoring was in outcomes in pregnant women, then patient selection could be restricted to women of child-bearing age.

4.3 Patient identification

4.2.1 See section C6.1.1.

4.2.2 It is vital that patients can be identified accurately. Inaccurate identification will result in:

4.2.2.1 duplicate entries in the database leading to inflated numbers in the cohort and inaccurate statistics;

4.2.2.2 difficulties in follow-up.

4.4 Other patient data

4.4.1 Age at the time of treatment (date of birth to help identification).

4.4.2 Sex.

4.4.3 Weight and height for body mass index.

4.4.4 Patient clinic identification number for file or card.

4.5 Background data

4.5.1 History of significant illness (e.g. liver disease, kidney disease).

4.5.2 Other diseases present at the time of treatment (e.g. tuberculosis, anaemia).

4.6 Controls or comparators

4.6.1 Proper control cohorts

Two treatment groups would need to be matched and treated under the same conditions at the same time in a blinded fashion. This would create an artificial situation and interfere with the recommendations for first-line treatment. Such a study would be a research project and would no longer be an observational (non-interventional) study. It would not be a true pharmacovigilance activity.

4.6.2 Comparator cohorts. A CEM programme involving two (or more) ARV regimens, given to patients in the same population, and which took into account drug substitution, might provide a useful comparison of the medicines involved. Comparisons could be made of two regimens in two groups of the same population over the same period, or of consecutive treatments in the same patients who have had drug substitutions or changed regimens. Because the patients in the different cohorts are not strict controls, comparisons would have to be made with caution due to the likely presence of confounders.

4.6.3 Pre-treatment control period. Before a decision is made to treat a new patient, a baseline assessment is undertaken and the patient is reviewed again after an interval (often one month), when a decision on whether or not to treat is made. For patients who are to be treated, any adverse events that occurred during the assessment period should be recorded. It is helpful to give patients a notebook in which they can record any health problems over this period.

These events recorded before treatment can serve as an accurate control for the events occurring after treatment. This would be the most satisfactory method of controlling for background noise.

5. Third step – acquiring the data

THE MEDICINES

5.1 Details of administration of ARVs

5.1.1 Treatment details:

5.1.1.1 name of each medicine: the standard abbreviations should be used for each medicine e.g. AZT, 3TC, NVP (see Annex 3, Table 1 for list of abbreviations);

5.1.1.2 the standard abbreviations for regimens may be recorded if this is more convenient (see Annex 3, Table 2);

5.1.1.2 total daily dose should be recorded for each medicine, even if the patient is receiving the standard adult regimen;

5.1.1.3 date of commencement of treatment of each medicine;

5.1.1.4 date of withdrawal or cessation of any medicine: if any, or all of the medicines were stopped temporarily for any reason, a stop date and a restart date should be recorded.

5.1.2 Treatment adherence:

5.1.2.1 record complete or incomplete adherence;

5.1.2.2 record reason(s) for incomplete adherence using codes in footnote.[1]

5.1.3 Reasons for cessation of ART:

5.1.3.1 poor adherence;

5.1.3.2 lost to follow-up;

5.1.3.3 death (give date & cause: see section F4.);

5.1.3.4 suspected adverse reaction/allergy;

[1] 1, toxicity/side-effects; 2, share with others; 3, forgot; 4, felt better; 5, too ill; 6, stigma/privacy issues; 7, drug out of stock; 8, patient lost/ran out of pills; 9, delivery/travel problems; 10, cost; 11, alcohol; 12, depression; 13, pill burden; 14, other.

5.1.3.5 lack of effect (based on clinical assessment or viral load);

5.1.3.6 other (describe).

5.1.4 Effectiveness:

5.1.4.1 did the patient's condition improve as expected ("yes" or "no");

5.1.4.2 if the patient's condition did not improve as expected, please comment.

5.2 Concomitant medicines

5.2.1 All medicines taken during ART, either in the short or long term, should be listed. This includes vaccines.

5.2.2 Record the following information on each concomitant medicine:

5.2.2.1 name: generic preferred;

5.2.2.2 any traditional medicine(s) ("yes" or "no");

5.2.2.3 indication for use;

5.2.2.4 dose and frequency of administration;

5.2.2.5 date started; if long term and the date is uncertain, record, "long term";

5.2.2.6 date stopped (record "continues" if not stopped).

5.2.3 In respect of taking **traditional medicines**, the questionnaires simply ask the patients to answer "yes" or "no". This is because many patients would not know the name of the traditional medicine they were taking. Many of these medicines have a number of poorly defined constituents of variable quality and quantity and a similar name may be used for quite different products. If the analysis did show an important event associated with the use of traditional medicine, then elucidating the problem would require a special research study. However, if CEM staff and the HIV clinicians believe that patients would know about those traditional medicines that are well recognized and commonly used, then these could be recorded. This would add some specificity, but recording them would need to be a local decision.

5.2.4 It is important to record **vaccines** as concomitant medicines, because of the possibility of adverse interactions with ARVs. Also, it is worth noting that the response to vaccines in immunocompromised patients is somewhat unpredictable.

5.3 Principles of event reporting

5.3.1 *All adverse events* are requested to be recorded and not just suspected adverse reactions. Clinicians or recorders should be asked to make no judgement on causality.

5.3.1.1 These events will be recorded on the "*Treatment review questionnaire*". The logistics of this will be described in section D5.7.

5.3.1.2 Normal clinical terms or descriptions should be used. There should be no attempt to apply the official adverse event terminology (see section D9.3).

5.3.1.3 Should a clinician wish to apply a term that meets an accepted definition, this should be done, but the term should be qualified as meeting the definition by recording "(defined)" alongside the term. These terms will then be entered into the database as meeting the definition. Any other use of the same term not qualified as "defined", will be entered and qualified as "not defined".

5.3.2 "*Adverse events*" (see definition section D1.1.1) are asked to be reported because there are **always** unexpected or unrecognized adverse reactions. If only suspected reactions are reported, then those which are unexpected and unrecognized are likely to be missed.

5.3.3 *All clinical events* experienced by each patient should be recorded. This includes unexpected improvement of concomitant disease (favourable event) as well as adverse events.

5.3.4 *Pre-treatment*: All events occurring in the assessment period (between the baseline assessment and treatment initiation) should be recorded, including those from the patient's diary. These control events will be recorded on the "*Treatment initiation questionnaire*".

5.3.5 *Post-treatment*: At follow-up visits any new events or worsening of pre-existing conditions that have occurred since treatment began should be recorded on the "*Treatment review questionnaire*".

5.4 What kind of events?

Health professionals should be asked to record the following types of events:

5.4.1 All **new** events even if minor.

5.4.2 **Change** in a pre-existing condition.

5.4.3 Abnormal **changes** in laboratory tests compared with a previous examination.

5.4.4 Lack of **effectiveness**.

5.4.5 **Admission** to hospital with date and cause.

5.4.6 The first observation of **pregnancy** of any duration.

5.4.7 An infant breastfed by a mother on ART (**lactation exposure**).

5.4.8 **Accidents**.

5.4.9 All **deaths** with date and cause.

5.4.10 Possible **interactions**.

5.4.10.1 Include pharmaceutical or traditional medicines.

5.4.10.2 Remember oral contraceptives and alcohol.

5.4.10.3 Be aware of the possibility of food–drug interactions.

5.5 Recording event details

5.5.1 *A brief description* of each event is usually all that is necessary. These event descriptions will be reviewed later by a Clinical Reviewer and standard adverse event terminology will be applied then. The clinician does not need to know, or refer to, the standard event terminology.

5.5.2 *Standardized codes* can be used for common events as per WHO guidelines for HIV care (see Table 2).[1]

5.6 Reporting forms (questionnaires)

There are three questionnaires for routine monitoring. The data elements are discussed in detail in section D6.2 (Annex 4). There are additional questionnaires for monitoring pregnancy (see section F2).

5.6.1 The baseline questionnaire

This is used to record:

5.6.1.1 patient details, including demographic data (not all of these are repeated in subsequent questionnaires);

5.6.1.2 any current treatment;

[1] Patient Monitoring Guidelines for HIV Care and ART, 2006.

TABLE 2

Standardized codes for common events

Commonly recognized	Opportunistic or other problems
Nausea	**Z**oster
Diarrhoea	**P**neumonia
Fatigue	**DE**mentia/Enceph
Headache	**Thrush** oral/vaginal
BN burning/numb/tingling	**DB** difficult breathing
Rash	**IRIS** Immune reconstitution inflammatory syndrome
Anaemia	**W**eight loss
ABdominal pain	**UD** urethral discharge
Jaundice	**PID** pelvic inflammatory disease
FAT changes	**GUD** genital ulcer disease
	Ulcers – mouth or other

5.6.1.3 past conditions of importance;

5.6.1.4 laboratory test results.

5.6.2 The treatment initiation questionnaire

This is used to record:

5.6.2.1 the above details; plus

5.6.2.2 any events during the pre-treatment control period;

5.6.2.3 comorbid conditions.

5.6.3 The treatment review questionnaire

5.6.1.2 This is the post-treatment (or follow-up) questionnaire. It is for recording the follow-up information on events and outcomes of treatment at each review.

5.6.1.3 A new questionnaire should be completed at each follow-up visit.

5.6.4 Local requirements

The questionnaires may need to be adapted for local use, in particular to give them a local flavour.

5.6.5 Standardization of questionnaires

Although the format of the questionnaires may be adapted to local prefer-

ences, it is important that the data fields remain unchanged. This will allow aggregation of data across regions or countries enabling valid comparisons. The international aggregation of data will also allow more powerful statistical analyses of the larger numbers in the combined cohorts. This includes **data mining** at the UMC.

5.7 Logistics of data recording

5.7.1 Background

HIV clinics are frequently under-resourced and over-busy. It is therefore extremely important to avoid adding to the burdensome demands on the clinicians and other health workers running the clinics. However it should be remembered that pharmacovigilance is an essential arm of patient care and when done properly, has the potential to **reduce risk and improve benefit** for the patients and ultimately to **reduce costs** to the system. This is achieved by the provision of data that will allow:

5.7.1.1 the identification of risk factors for serious reactions. This will enable better selection of medicines for individual patients and avoidance of troublesome and costly adverse reactions;

5.7.1.2 the early identification of previously unrecognized adverse reactions, which will allow preventive action that will minimize the effect of these problems in the patient population and the adverse publicity that can arise from a delay in recognition;

5.7.1.3 the measurement of the comparative safety of different medicines and regimens of ART.

5.7.2 Planning

5.7.2.1 Administrators and programme managers need to be aware of these advantages and provide the resources to undertake adequate pharmacovigilance.

5.7.2.2 CEM can provide the necessary data better than spontaneous reporting and do so relatively quickly.

5.7.3 Recording of data

5.7.3.1 With CEM in the IMMP and PEM, the data are recorded from existing records following each patient visit. Where clinics have an adequate system for recording events, this could be done with ART monitoring. This may require the recording of types of events that are not normally recorded (see requirements for event recording, section D1.1). Clinical staff would need to be trained to perform this more comprehensive re-

cording and would need to understand that this goes beyond the advice often found in guidelines to keep the recording of data to an essential minimum. All events data are necessary.

- Recording data from the patient diary will need to be undertaken while the patient is still present. This also provides the opportunity for clarifying the meaning of any entries.
- Recording of the events from existing records should be performed as soon as possible after the patient consultation.
- Recording should be done by a health professional who is familiar with clinical terminology (e.g. a nurse) and this person should be trained and employed for this work (under the title of "data recorder").
- At sites with advanced facilities, it may be possible to record or extract the required data electronically.

5.7.3.2 Where clinic records are inadequate for the data extraction required, other methods of recording will need to be developed to suit the local site. This should be done in consultation with clinic staff. Some possibilities are:

- the recording of non-clinical data (e.g. patient ID and demographics) by support staff while the recording of clinical data is done by the clinicians;
- the recording of non-clinical data by support staff while the recording of clinical data given by the clinician during the consultation process is done by a trained data recorder;
- the recording of all data on medicines by the pharmacist or a pharmacist assistant.

5.7.3.3 Where the workload of a clinic cannot cope with daily recording, it might be preferable to undertake monitoring only at certain clinic sessions e.g. every morning, or on specific days of the week such as Tuesdays and Thursdays, or on the first 20 patients each day.

5.7.4 Sentinel sites

In planning CEM, sentinel sites should be chosen where resources are adequate, or can be provided, and where staff are willing to participate with appropriate support.

5.7.5 Duplicate pads

Consideration should be given to printing the questionnaires in pads on duplicate self-copying (NCR) paper.

5.7.5.1 Separate pads would be needed for each of the three questionnaires.

5.7.5.2 It would be an advantage to have them colour-coded.

5.7.5.3 The forms should look as attractive and professional as possible. This communicates that the system is professionally organized and encourages compliance with the programme.

5.7.5.3 When the forms are completed in the clinic, the top copy of each form should be sent to the PvC for data processing (by the CEM Focal Person) and the duplicate copy retained in the health facility with the patient's record, where possible, or in another specified location.

5.7.5.4 A standard operating procedure (SOP) would need to be developed for collecting, storing and forwarding the forms.

5.7.5.5 An SOP, properly supervised, should:

- reduce the likelihood that forms will be lost;
- ensure that copies of the questionnaires are retained in the health facility for reference;
- ensure that the questionnaires would reach the PvC soon after completion and the data manager for the CEM programme would have the opportunity to instigate procedures for checking up on follow-up questionnaires not received at the expected time.

5.8 Frequency and duration of monitoring

5.8.1 Routine monitoring

5.8.1.2 The frequency of recording monitoring data will be mainly dependent on the normal schedule of assessment and follow-up at the clinic

5.8.1.3 If patients are requested to return monthly or quarterly, then events should be recorded at these scheduled visits.

5.8.1.4 When the patient's condition and treatment has become stable, recording could be reduced to 6-monthly or annually.

This would be dependent on the decision of the CEM team in consultation with the clinical team.

5.8.2 Termination of routine monitoring

The data from monitoring should be analysed and reviewed at regular intervals, preferably no less frequently than every three months. Trends can then be identified and when it is clear that no new problems are arising, a decision can be made to stop routine monitoring. In view of the known delayed onset of some toxicities, it is suggested that routine monitoring continue for at least four years.

5.8.3 Long-term monitoring

There are a number of reasons why certain subgroups of the cohort should have long-term and perhaps indefinite monitoring. There is a need to:

5.8.3.1 monitor patients with **specific toxicities**, in order to understand better the natural history of the problems;

5.8.3.2 monitor patients with specific **comorbidities** e.g. tuberculosis. Greater numbers may be required to establish the pattern of long-term outcomes and give sufficient statistical power to enable risk factors to be identified and determine possible interactions between ART and therapy for tuberculosis or other diseases;

5.8.3.3 to define more clearly adverse reactions and the risk factors specific to **children**. Comparison with the adults in the cohort may not be definitive if the number of children in the original cohort is small;

5.8.3.4 continue to monitor patients on **specific regimens** or with specific substitutions to achieve sufficient numbers to make valid comparisons;

5.8.3.5 monitor women of child-bearing potential to achieve greater numbers of subjects who become pregnant while on ART and enable assessment of the outcome.

5.8.4 Non-attenders

Good coordination with the clinic health workers needs to be established in order to obtain information on any events that occur in patients who have lost mobility and are unable to attend the clinic, or have been admitted to hospital, or have died, or have been lost to follow-up for some other reason, which could include severe or serious adverse reactions. An SOP should be developed to facilitate this.

5.9 Reasons for lack of adherence

It is important to document the reasons for incomplete adherence or non-adherence to the treatment schedule. These should be recorded on the *Treatment review questionnaire*. WHO guidelines suggest the use of the following codes:

1. toxicity/side-effects
2. share with others
3. forgot
4. felt better
5. too ill
6. stigma, disclosure, privacy issues
7. drug stock out—dispensary
8. patient lost/ran out of pills
9. delivery/travel problems
10. inability to pay
11. alcohol
12. depression
13. other … describe.

5.10 How and where to send the completed questionnaires

5.10.1 The completed questionnaires need to be sent to the national or regional PvC according to an agreed procedure. There the events will be assessed and the information entered into a database.

5.10.2 The method of sending the questionnaires needs to be planned with each health facility, ranging from hospitals to rural clinics and an SOP prepared for each facility.

5.10.2.1 It may be desirable for rural clinics to send their reports to district hospitals and for district hospitals to send them to referral hospitals which will then send them to the PvC. However, some other method may suit local circumstances better. An appropriate chain of communication needs to be established and everyone involved should be well informed about it.

5.10.2.2 The questionnaires should be stored securely so that they cannot be accessed by unauthorized people.

5.10.2.3 An appropriate frequency for sending the reports needs to be established, e.g. weekly, and the role of checking on the transfer of the reports along the chain needs to be assigned to a suitable person (e.g. Field Coordinator).

5.10.2.4 An SOP should be prepared and made known to everyone involved.

5.11 Record linkage

Record linkage is another method of active surveillance that may be used to supplement or check information received on the CEM questionnaires.

5.11.1 This is a method of searching different health databases electronically using unique patient identifiers.

5.11.2 The unique patient identifiers (or national health numbers) must be in use nationally to enable national registers of deaths or diseases to be searched. The identifying health number must be recorded with the patient details in the cohort database.

5.11.3 Examples of databases that may be available for searching using the health identifiers are:

5.11.3.1 register of deaths;

5.11.3.2 register of congenital abnormalities;

5.11.3.3 cancer registers;

5.11.3.4 other specialist registers, e.g. myocardial infarction.

5.11.4 In the absence of national numbers, other identifying numbers (e.g. hospital numbers) if available, can be recorded in the patient cohort data. It would then be possible to use these numbers to search registers maintained by the hospital (e.g. a teaching hospital) or another facility that has health (or disease) registers.

6. Database for CEM

6.1 Choice of database

6.1.1 The UMC has developed CemFlow for this purpose and it is recommended. A broadband Internet connection is necessary. WHO is investigating the possibility of providing good Internet access to those PvCs that do not have it. The same principles apply to the use of CemFlow as to VigiFlow used for spontaneous reporting (see section A10.2). CemFlow provides for entry of cohort data as well as the events and also provides programmes for statistical analyses.

6.1.2 Microsoft Access could be used, but is difficult to manage and not wholly satisfactory.

6.1.3 Purpose-built databases can be programmed using the software, SAS. This requires a person with expertise in this software.

6.1.4 A relational database is desirable that can link separate smaller databases for analysis as required. A single database with all the data would be too big to manage.

6.2 Data elements/fields

6.2.1 It is desirable to have separate databases for the:

6.2.1.1 cohorts with all patient data;

6.2.1.2 medicines with all details of use;

6.2.1.3 events with dates and outcomes;

6.2.1.4 reporters (treatment providers) with contact details.

6.2.2 Fields required in the database need to allow for entry of all the data elements included in the questionnaires. Some of the data from the questionnaires require the application of dictionary terms and codes and also relationship assessment (see section G).

6.2.3 Data elements included are:

6.2.3.1 Patient

- name, first name and family name;
- unique ID number (see 6.2.3.2);
- clinic number;
- address or contact details;
- gender;
- date of birth and/or age;
- weight and height;
- pregnancy status, if applicable.

6.2.3.2 Patient ID numbers

There are usually two or more patient ID numbers available which allow patients to be identified accurately. This helps to avoid confusion between the identity of patients in the database making sure the correct data are assigned to the correct patient. Use of ID numbers also helps to keep cohort numbers accurate and hence the statistics derived from the data.

- **Unique country ID numbers** allow patient records to be accessed, and where possible, linked to other medical information at a higher level for analysis at the district or country

level (record linkage – see section D5.11). To avoid providing multiple unique numbers to one person, it is necessary to be able to match patients to their prior records and ID. This requires the use of other identifying information such as name, date of birth, telephone number, address and date ART was started, to be stored with the assigned unique number. These personal data are also necessary when a person's unique number cannot be found. The unique patient number is a single identifier that is permanently assigned and cannot be applied to any other person. Patients may already have unique numbers for general medical care, such as a national health number or patient medical card, or from receipt of other social services within a country.

- The **patient clinic ID number** is the patient record or chart number (non-unique) that most health facilities issue upon patient registration. This enables the correct patient records to be retrieved.
- Both numbers should be recorded on the questionnaires.
- In analyses and when information is shared within the country, use of the ID numbers without personal data helps to preserve patient identity and privacy. The ID numbers are not used in published data.

6.2.3.3 Medicine(s)

Medicines must be identified correctly and recorded appropriately as follows:

- identified using the WHO Drug Dictionary name and Anatomic Therapeutic Chemical (ATC) code;
- indication for use (WHO International classification of diseases version 10 (ICD-10) code);
- dose;
- date of commencement;
- quantity supplied;
- instructions for use;
- date of stopping treatment;
- date of withdrawal;
- date of dose reduction;
- date of rechallenge; and
- concomitant medicines with details of administration and dates.

6.2.3.4 Events
(see sections D.1.1 and D.5.3).

- **report number**: each treatment review questionnaire that has events recorded should be given a report number and this number should be recorded with the events. The report numbers for CEM should link with the report numbering system given for ICSRs (spontaneous reports) in the PvC;
- event term(s) from the events dictionary;
- date of onset;
- effect of dechallenge (withdrawal of medicine);
- effect of rechallenge;
- severity;[1]
- seriousness (see section A2.3);
- outcome;
- relationship.

6.2.3.4 Contact details of CEM Focal Person at the health facility (or treatment provider/reporter):

- name;
- status (e.g. doctor or nurse);
- hospital or clinic name, telephone and fax number.

7. Maximizing the reporting rate

7.1 Prepare the ground

In all the planning phases and communications with health professionals, health workers and public health staff, it is important to try to develop a culture of collaboration: working together for the successful management of ART in the safest possible way for the patients.

7.2 Removing barriers to reporting

The following means of removing barriers need to be considered.

7.2.1 Ensure an adequate supply of readily available questionnaires.

7.2.2 Make sure everyone is adequately briefed on the importance and value of CEM and understands the basic methodology.

7.2.3 Arrange the completion of the forms in such a way as to minimize any disruption to the normal flow of work in the clinic (see section D5.7.3).

[1] Severity is coded as not severe, mild, moderate, or severe.

7.2.4 Don't ask for information that is not absolutely necessary for pharmacovigilance purposes.

7.2.5 Don't ask for information that might take a long time to find, e.g. batch numbers, unless it is very important.

7.3 Other health facilities

Patients may need to visit health facilities other than their regular HIV clinic. For event reporting to be complete, reports of all health events are needed from these facilities. It is suggested that patients be given an ID card with instructions to any other health professional to contact the patient's regular clinic and advise them of any problem(s), so that they can be recorded in the patient's data and included in the monitoring programme. The essential information to be included on the card is shown in Annex 5. The card should be designed locally and printed in the local language.

7.4 Feedback

Good feedback will encourage compliance by the health professionals and health workers. They will need regular information to be sent to them by the PvC. This information needs to be relevant and helpful to their work. Occasional meetings to discuss the results are valuable.

8. General advice and information

8.1 Don't ask for too much

8.1.1 The more you ask for the less you will get.

8.1.2 All events are essential, but the necessity for other data needs to be weighed carefully.

8.1.3 Increased data increases the workload and the cost.

8.1.4 Some information is best requested by follow-up when the necessity for it can be explained and interest created by the problem being explored.

8.2 Non-serious events

It is important to include these because:

8.2.1 They might indicate a serious problem.

8.2.2 They might affect adherence, e.g. nausea.

8.2.3 If common, they might be more important to public health than rare, but serious problems.

8.3 Be open-minded

8.3.1 Predictions of safety, if based only on spontaneous reporting, are unreliable.

8.3.2 Unexpected reactions will occur.

8.3.3 Avoid preconceived ideas on safety.

8.3.4 **All events data** should be collected and analysed in a totally **objective** manner.

8.4 Privacy

8.4.1 Given basic precautions to maintain confidentiality, patients will give greater priority to safety concerns.

8.4.2 Security and confidentiality of data is the essential requirement. Other ethical requirements should not prevent CEM taking place or reduce its functionality, because it is unethical not to pursue those methods that are essential to safety assessment and the protection of patients.

8.4.3 Ethical issues are discussed in section M.2.

9. Fourth step — clinical review

This involves the following activities at the monitoring centre:

- assessing the clinical details and determining the appropriate event terms;
- determining the duration to onset of each event;
- recording data on dechallenge and rechallenge (if any);
- determining severity and seriousness;
- recording the outcome of each event;
- undertaking a relationship assessment for each event as the first step in establishing causality.

9.1 The event should be specific to be acceptable for recording

For example, sometimes a "stomach upset" is reported, but this description is too vague. It could mean dyspepsia, nausea, vomiting, diarrhoea, or some other specific event.

9.2 Determining the event term

9.2.1 A person with clinical expertise (the CEM Clinical Supervisor) in the CEM unit of the PvC should review the details of the events described on the questionnaire.

9.2.2 The first decision to be made is which Clinical Group(s) (equivalent to System Organ Class), would be the most appropriate in which to record the event(s). e.g. alimentary or respiratory.

9.2.3 The most appropriate term should then be selected from the particular Clinical Group in the WHO event dictionary.

9.2.4 With CemFlow the event terms are available online and are easily found and selected.

9.2.5 If however, there seems to be no appropriate term for a reported event, a new term can be entered. In choosing a new term, a standard medical term should be selected from ICD 10, another dictionary (e.g. MedDRA or WHO-ART) or from a textbook or the literature. This additional term is reviewed during dictionary maintenance and added to the dictionary if approved, or another appropriate term applied. Definitions will be added as necessary.

9.2.6 If it is not possible to use CemFlow, the selected terms should be recorded for later data entry on a coding sheet (see section E3.4.2 and Annex 6).

9.3 The events dictionary

9.3.1 The need

The need for an **events** dictionary arises because the readily available dictionaries are **reaction** dictionaries related to the spontaneous reporting of suspected adverse reactions rather than of events.

9.3.2 Standard terminology

It is important to use standard terms so that data can be compared between CEM programmes run in different regions or countries and/or at different times.

9.3.3 Why have a specific events dictionary?

9.3.3.1 Event monitoring requires a dictionary of clinical events, many of which will not be reactions.

9.3.3.2 Many event terms are not found in standard reaction dictionaries (WHO-ART, MedDRA).

9.3.3.3 Clinical events, rather than suspected reactions, need to be recorded in order to identify unexpected reactions.

9.3.3.4 Event monitoring of new medicines in developing countries will produce many new event terms that are not in standard (Western) reaction dictionaries because of:

- different combinations of ARVs used in a public health approach adopted by WHO in resource-limited countries;
- different medicines being used in common practice given concomitantly with ART, e.g. artemisinin combination therapies for malaria;
- different comorbid conditions e.g. malnutrition or parasitic infestations;
- the common use of traditional medicines;
- different ethnicity, diet and living conditions.

9.3.4 The structure of the dictionary

9.3.4.1 Event terms are organized in a hierarchical structure of five levels that arrange the terms in clinically related groupings through to the lowest level.

9.3.4.2 The structure is used to collate and display the events in a clinically meaningful manner.

9.3.4.3 The major Clinical Categories are listed in Annex 7.

9.3.4.4 The Clinical Categories include Deaths, Pregnancy exposure, Lactation exposure and Concomitant medicines so that these will be displayed routinely after automated collation.

9.3.5 The clinical and epidemiological value of the dictionary

9.3.5.1 To create a clinical collation of events that enables a visualization of the pattern of morbidity in the cohort.

9.3.5.2 To present a clinical collation of events that provides a key to rapid signal identification.

9.3.5.3 The listings of collated events can be presented with rates for individual events and for their groupings.

9.3.5.2 The collation of events from the control period provides a picture of the background morbidity in the community.

9.4 Dictionary maintenance

9.4.1 New terms may be added to the country CEM database by the clinical reviewers of the reports, but when the reports with new terms are forwarded to the UMC, these new terms will be flagged for consideration by a central standardizing committee, which will give feedback on the terms approved. This committee will consult with HIV/AIDS experts as appropriate to help determine the best term.

9.4.2 The dictionary will be rapidly adaptable to meet the day-to-day needs of the event monitoring programmes.

9.4.3 Some definitions are built into the dictionary and these will be added to. For HIV-specific terms, definitions will be sought from HIV/AIDS experts.

9.4.4 Any new *reaction* terms (as opposed to incidents) found necessary will be included in WHO-ART and mapped to MedDRA. Where there are no matching terms in MedDRA, a request will be made for their inclusion.

9.5 Seriousness

9.5.1 This is defined in section C2.3 and C6.2.2 and each event should be routinely recorded as either serious or not serious.

9.5.2 If serious, then the reason for this choice of description should be given. Codes can be used to indicate this e.g. "H" for hospitalization or prolongation of hospital stay. Suggested codes are listed in the footnote.[1]

9.6 Severity

9.6.1 Severity does not have the same meaning as seriousness. A patient can experience a severe event that is not serious e.g. pruritus.

9.6.2 Severity is a subjective assessment made by the patient and/or the clinician. Although subjective, it is nevertheless useful in identifying reactions that may affect adherence.

9.6.3 There is no international agreement on the use of the term severity, but one recommendation for recording severity in WHO HIV guidelines is to classify as "not severe, mild, moderate, severe".

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[1] Seriousness codes: D, died; L, life threatening; H, hospitalization; Dis, permanent disability; C, congenital anomaly.

9.7 Outcome of the event

9.7.1 The types of outcome to be recorded are as follows, along with codes that can be used to simplify recording:

R1 resolved;

R2 resolving;

RS resolved with sequelae;

NR not resolved;

DR died due to adverse reaction;

DC died – medicine may be contributory;

DN died – not related to medicine;

DU died – cause unknown.

9.7.2 Normally recording the outcome is a matter of recording the outcome entered on the questionnaire, but at times clinical judgement is required, e.g. when recording deaths.

9.8 Relationship to the medicine/regimen

This is discussed in section G.

E. Data processing

1. Data entry

1.1 Requirements

1.1.1 Data must be accurate.

1.1.2 Data processors must be trained and supervised until their level of skill is acceptable.

1.1.3 Data processors need to be given good tools (a good computer and suitable office furniture). It is an exacting job.

1.1.4 Share the vision and share the results with the data processors. Help them to see that they are a vital part of the team.

1.2 Standard formats

The use of standard formats is a means of reducing error.

1.2.1 Methods

1.2.1.1 Use input masks so that anything other than predetermined terms will be rejected.

1.2.1.2 Use field controls so that certain values can only be entered in a selected way.

1.2.1.3 Use drop-down lists for standard choices.

1.2.2 Examples

1.2.2.1 Date format: dd/mm/yyyy.

1.2.2.2 Numbers: restrict number of digits to what is appropriate for values entered into particular fields, e.g. age – restrict to 2 digits.

1.2.2.3 Use WHO Drug Dictionary codes for medicines and ICD-10 codes for diseases.

1.2.2.4 Drop-down lists: use M or F for sex; doses – mg, ml, etc; names of hospitals and clinics; units for laboratory values.

2. Quality control

2.1 Control at entry

2.1.1 Use field controls and standard formats as in E1.2.

2.1.2 The use of codes, e.g. ICD-10 or ATC codes results in fewer errors than does typing in names.

2.2 Systematic checks

2.2.1 Print lists of data regularly e.g. every morning or every week (depending on the volume of data) and do a manual check of the different fields. Examples of what to look for include:

2.2.1.1 dates that are improbable;

2.2.1.2 male sex with female name;

2.2.1.3 similar names (e.g. Joe and Joseph) with the same date of birth who could be the same patient.

2.2.2 Sort the data by important fields in turn and check each printout.

2.2.3 Apparent inaccuracies need to be checked against the original data which may need to be corrected.

2.2.4 The computer counts slight differences separately and will inflate the numbers if there are duplications due to inaccuracies.

3. Coding of medicines and diseases

This is only necessary if working in the absence of CemFlow.

3.1 WHO Drug Dictionary

Select drug names or codes from the WHO Drug Dictionary.

3.2 ICD-10

Use the ICD-10 for diseases that are recorded as indications for treatment or diseases recorded in the medical history. (The ICD is also a useful source of acceptable event names.) These codes are accessible in CemFlow.

3.3 Standardized recording of event details

3.3.1 CemFlow

CemFlow is the preferred method of data entry. The clinical reviewer can enter clinical details directly on a "reviewer's screen" during the review process. The head of the PvC or the CEM Clinical Coordinator can apply to the UMC for access and user registration for CemFlow (email: info@who-umc.org).

3.3.2 Coding sheet

In the absence of CemFlow, a coding sheet is a useful tool for facilitating review and recording the clinical details in a report. An example is provided in Annex 6.

3.4.3.1 The coding sheet should be completed before data entry. This speeds up data entry and reduces error. With a completed coding sheet a data processor is able to enter these clinical details instead of the clinical reviewer.

3.4.2 Use of CemFlow or a coding sheet by reviewers ensures a systematic and standard approach to reviewing the events reported on the questionnaires.

4. Using CemFlow

Data processing as described above is very much simplified with the use of CemFlow.

4.1 It has built-in drop-down lists for data entry.

4.2 It has built-in quality control checks.

4.3 There is built-in access to dictionaries and codes.

4.4 It requires a standardized approach to data entry including the reviewer's assessment of each event.

4.5 With the use of CemFlow, a coding sheet is not necessary.

5. Collating and summarizing the events

This should be seen as a regular function of the data manager.

5.1 The events are sorted by the event dictionary codes.

5.2 When a printout is made, the events listing will reveal the clinical pattern of the events that have occurred.

5.3 This should be done at regular intervals during CEM – monthly is suggested.

5.4 This collated events listing is one of the programmed reports on CemFlow and can be produced at any stage.

5.5 This events collation should incorporate the following fields:

5.5.1 event;

5.5.2 sex;

5.5.3 age at the time of the event;

5.5.4 dose;

5.5.5 duration to onset in days, hours or minutes;

5.5.6 relationship, coded as follows: 1 (certain), 2 (probable), 3 (possible), 4 (unlikely), 5 (unclassified), 6 (unclassifiable);

5.5.7 report ID number;

5.5.8 death;

5.5.9 withdrawal of medicine.

5.6 The collation will provide the earliest means of identifying signals simply by observation of the clinical patterns of events. This method of signal identification is very sensitive.

5.7 A sample page of **collated events** can be seen in Annex 8.

5.8 Constructing **event/risk profiles**:

5.8.1 This is done by graphically representing the rates of events in each clinical category, but can also be performed on groups of related events within a category.

5.8.2 It is particularly useful for comparing two or more medicines or regimens.

5.8.3 A sample page of comparative event profiles can be seen in Annex 9.

5.8.4 To develop a risk profile, only those events coded as having a relationship of 1, 2 or 3 should be included. This results in a profile of those events with a plausible relationship and illustrates the actual risk pattern better than an events profile which includes all events, including those with an "unlikely" relationship.

F. Special types of event

1. Serious events

1.1 These are defined in sections C2.3 and C6.2. See also D9.4.

1.2 Details of serious events should be sent immediately to the HIV programme manager and the CEM Clinical Reviewer in the PvC where they will be fully assessed and appropriate action taken.

1.3 A process needs to be defined for each health facility to follow so that there is no delay. National drug regulatory authorities often have in place standard operating procedures and clear timelines for transmission of case-report forms in case of serious adverse events. Regulatory requirements for reporting should be integrated into the procedures for CEM.

2. Pregnancies

2.1 Background

2.1.1 "*While it may be desirable to initiate ART after the first trimester in order to minimize the potential for teratogenicity, the benefit of early therapy clearly outweighs any potential foetal risks and therapy should be initiated in such cases.*" (*Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach*. WHO. 2006:45)

2.1.1 The stimulus for pharmacovigilance was the thalidomide disaster. Initially the only method available was spontaneous reporting. This methodology could identify a major effect, but less frequent effects could go unidentified, at least for a time.

2.1.2 A very important aspect of CEM of ARVs is obtaining more information on safety in pregnancy, particularly with new medicines and those with which there has been limited experience. In general, "*There is only limited information about the safety of ART for pregnant women and their infants.*" (Quoted from above reference.)

2.1.4 The success of obtaining outcomes of exposure during pregnancy depends on the vigour of follow up.

2.2 CEM of pregnancy

2.2.1 Three follow-up questionnaires have been designed to facilitate the gathering of outcome information following exposure to ARVs during pregnancy.

2.2.1.1 Initial Pregnancy Questionnaire (A) Annex 10.
This form is to record baseline details on pregnancy when the woman is diagnosed as pregnant while on ART, or when ART is initiated during pregnancy. Completing the questionnaire and forwarding it for data entry will help ensure follow-up. Alerts can be programmed for the expected follow-up time and appropriate action taken if a progress questionnaire does not come through.

2.2.1.2 Pregnancy Progress Questionnaire (B) Annex 10.
This questionnaire is designed to detect abnormalities of the progress of the pregnancy, including foetal death and pregnancy-related problems in the woman. It should be completed at intervals during the pregnancy, either at each follow-up visit to the HIV clinic or at the antenatal clinic, according to the protocol established locally.

2.2.1.3 Pregnancy Outcome Questionnaire (C) Annex 10.
It is recommended that the infant is examined at birth or postnatally, at three months and at one year. Ideally, an examination by a paediatrician at one year should be undertaken with the aim of detecting any major internal abnormalities e.g. cardiac abnormalities. The examinations at three months and one year serve as additional checks, which will be of value because some congenital abnormalities are not obvious at birth, or if missed at birth, should be identified later.

2.2.2 All women who are known to be pregnant on ART should be followed up to find out the outcome of the pregnancy and the health status of the infant.

2.2.2.1 An SOP needs to be developed for each site where monitoring is taking place to ensure that every woman known to be pregnant is followed up by a health worker using the Pregnancy Progress Questionnaire and the Pregnancy Outcome Questionnaire.

2.2.2.2 Coordination and collaboration should be developed with antenatal, birthing and paediatric units.

2.2.4 At delivery and/or during a postnatal visit, the Pregnancy Outcome Questionnaire should be completed.

2.2.4.1 An SOP needs to be developed for each health facility to ensure that the Pregnancy Outcome Questionnaire is completed for every woman in the cohort who has given birth and that it is returned to the PvC.

2.2.4.2 Coordination and collaboration should be developed with the birthing and paediatric units.

2.3 Pregnancy register

2.3.3 The most convenient way of compiling a pregnancy register is to enter details of all pregnancies into the special Clinical Category, "*Pregnancy exposure*" in the events database. (This will happen automatically with CemFlow.) The event (pregnancy) is coded for this at the time of data entry. This category should be reviewed with the regular general collation of events and as required.

2.3.4 The fields that should be incorporated in the pregnancy register are:

2.3.4.1 ID details and report number;

2.3.4.2 age of mother;

2.3.4.3 duration of pregnancy on date of first exposure to ARVs;

2.3.4.4 outcome of pregnancy, including miscarriage or stillbirth;

2.3.4.5 duration of pregnancy at parturition;

2.3.4.4 outcome for fetus or newborn.

2.3.5 Any congenital abnormalities should be reported immediately to the clinical coordinator/reviewer for CEM at the PvC who should in turn, advise the HIV programme manager. Further investigation should follow.

2.3.6 The CEM clinical reviewer in the PvC should review the register regularly and ensure that all follow-up procedures have been undertaken, or attempted. An SOP should be developed for this.

2.4 Expectations from CEM monitoring of pregnancies

2.4.1 Using a CEM pregnancy register cannot exclude teratogenicity and is unlikely to confirm any particular congenital abnormality as being due to the medicines taken. This requires investigation by a specialist team.

2.4.2 A CEM pregnancy register will function as a case-finding programme. If there are several reports of congenital abnormality of a similar type, this can signal a possible teratogenic effect, which would need to be investigated further.

2.4.3 An unexpectedly high number of abnormalities of a similar type (compare thalidomide) could give strong evidence of a teratogenic effect and a general alert and regulatory action might be warranted.

2.4.4 If there are several reports of congenital abnormality of a similar type, data analysis might be able to point to a suspect regimen or medicine.

2.4.5 Depending in part on the numbers of pregnant women monitored, the absence of any apparent congenital abnormalities is reassuring, but is not conclusive of safety, particularly from uncommon problems.

2.4.6 CEM should signal common problems, which, of course, are more important than uncommon problems, because they affect more infants.

2.4.7 Rates of any congenital abnormality can be compared with background rates for that country or region, if these are available.

2.5 Verification of drug-effect

2.5.1 If congenital abnormalities are noted in any infant, then this finding should be followed up in an attempt to establish causality. This is a specialist activity that should be initiated by the PvC in consultation with its Expert Safety Review Panel (Advisory Committee)[1] and/or the WHO programme on pregnancy registries.

2.5.2 A specialized pregnancy register, which could be used to conduct studies on reports received including a control cohort, would be needed to validate a signal or establish an effect which is uncommon.

2.6 WHO pregnancy registry

2.6.1 The WHO Special Programme for Research and Training in Tropical Diseases and the WHO department "*Making Pregnancy Safer*" are assessing the feasibility of setting up a pregnancy registry in Africa. A protocol is available for countries interested in incorporating such a registry into their programmes.[2] The registry is being tested in several countries.

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[1] The Expert Safety Review Panel (or Advisory Committee) is a committee of experts that considers important safety issues and gives advice to the PvC and regulatory authority. The Committee's composition and role is described in *The safety of medicines in public health programmes: pharmacovigilance an essential tool*. World Health Organization 2006:38.

[2] It can be obtained from TDR: http://apps.who.int/tdr/

2.6.2 The basic methodology is that of a controlled prospective observational cohort study of randomly selected pregnant women with control cohorts.

2.6.3 Such a programme is not normal pharmacovigilance, and health professionals responsible for ART should consult the relevant WHO department for two possible reasons:

2.6.3.1 to consider developing such a programme for women of childbearing potential on ART;

2.6.3.2 to offer collaboration and request assistance in running a CEM pregnancy register. Collaboration could include:

- WHO training of staff in appropriate follow-up procedures;
- WHO offering trained staff to undertake or assist with follow-up;
- WHO providing training of staff in surface examination for the detection of major congenital abnormalities;
- WHO advice on referral to a specialist investigation team to follow up a signal;
- sharing of the CEM data.

3. Lactation exposure

3.1.1 Questions about exposure of an infant to breast milk from a woman on ART are included in the questionnaires.

3.1.2 At follow-up, women on ART who are breastfeeding need to be asked about any events they have observed in their infant.

3.1.3 The outcome for every infant exposed during lactation should be recorded. If there have been no events, it is important to record, "*no effect*" as the outcome.

3.1.4 Details of exposure during lactation should be incorporated in the special clinical category called "*Lactation exposure*" at the time of data entry in order to establish a register with outcomes.

4. Deaths

4.1 All deaths should be followed up to assess the cause, even if it seems most unlikely that death was related to the medicine.

4.2 Deaths should be entered in a special clinical category at data entry to compile a register for regular review with each collation of events. This facilitates assessment. A sample listing of deaths is included in Annex 11.

4.3 With CEM, death rates can be calculated. This has particular advantages.

4.3.1 Importantly, death rates can be used to measure changes in outcomes.

4.3.2 Death rates can be compared between comparators. Differences may demonstrate greater effectiveness or greater safety. Numbers need to be adequate to make valid comparisons.

5. Lack of efficacy

5.1 Event terms

51.1 Lack of expected efficacy should always be recorded as an event. The following event terms should be used as appropriate:

5.1.1.1 "medicine ineffective";

5.1.1.2 "therapeutic response decreased".

5.2 Reasons for lack of efficacy

5.2.1 These are important events to record. Possible reasons for lack of effect are as follows:

5.2.1.1 did not retain the medication because of vomiting or severe diarrhoea;

5.2.1.2 lack of adherence to treatment schedule;

5.2.1.3 inadequate dose;

5.2.1.4 poor quality medication;

5.2.1.5 counterfeit medication;

5.2.1.6 incorrect diagnosis;

5.2.1.7 interactions reducing blood levels;

5.2.1.8 drug resistance.

6. Late onset reactions

6.1 A number of important and serious adverse reactions to ART are late in onset or progressively worsen over time e.g. lipodystrophy.

6.2 Because the complete evolution of some of these problems is not fully characterized, a decision may be made by the clinical programme managers to extend monitoring of these particular patients until the natural history of the problem is evident or until the risks to the patients are unacceptable.

6.3 In the latter case a decision may be made to monitor these patients after the suspect treatment is withdrawn in order to develop an understanding of the degree of reversibility of the problem.

6.4 Special event terms and definitions may be needed to record changes as a toxicity progresses. The clinical experts should suggest what terms are needed and they can be added to the event dictionary.

7. Concomitant morbid conditions

7.1 Patients may be more susceptible to particular adverse reactions if they also have other health problems, either because of the concomitant condition or from the interaction of the ART with medicines being used to treat the other condition(s). Examples of concomitant illnesses that may result in such problems are: tuberculosis, malnutrition and malaria.

7.2 Concomitant conditions should therefore always be recorded and they can then be tested statistically as risk factors for events of interest.

G. Relationship/causality assessment

1. Background

1.1 Two basic questions

These questions need to be addressed separately.

1.1.1 Is there a convincing relationship between the drug and the event?

1.1.2 Did the drug actually cause the event?

1.2 Objective and subjective assessments

1.2.1 The objective phase

This takes into account actual observations and establishes the **relationship** (see sections G.2 and G.4, below).

1.2.2 The subjective phase

This is the process of making an attempt to establish a firm opinion about **causality** in those events for which a close relationship has been established. It takes into account the plausibility of the drug being the cause of the event, after having considered the (known) pharmacology, other experience with the medicine or related medicines, and inferences made from epidemiological observations and statistical evaluations (see section I3 and J2.5).

1.3 General understanding

1.3.1 Establishing causality is a process which begins by examining the relationship between the drug and the event.

1.3.2 The relationship of a single case-report can be established, but it may not be possible to establish a firm opinion on causality until a collection of such reports is assessed or new knowledge is gained.

1.3.3 The ultimate goal of assessment of each event, or a cluster of events being treated as a signal, is an answer to the question: *Did the drug cause the event(s)*? Yes or no?

1.3.4 Causality for individual reports, even those with a close relationship, can seldom be established beyond doubt and our assessments are based on probability.

1.3.5 A causality assessment should be seen as provisional and subject to change in the light of further information on the case, or new knowledge coming from other sources.

2. Factors to consider when assessing the relationship between drug and event

2.1 Did the event begin *before* the patient commenced the medicine?

This may seem an obvious consideration, but reports are received in which this has not been taken into account, and a careful check has then revealed that the event preceded the use of the suspect medicine and therefore there was no relationship.

2.2 Is there any other possible cause for the event?

2.2.1 Could the event be due to the illness being treated?

2.2.2 Could it be due to some other co-existent disease?

2.2.3 Could it be due to some other medicine being used concurrently?

2.3 Is the duration to onset of the event plausible?

2.3.1 Is the event likely to have occurred in the time frame in question?

2.3.2 Did it occur too quickly to be related to the particular medicine, taking into account its pharmacological action?

2.3.3 Did the patient take the medicine for a long time without any problems? (Delayed reactions after long-term exposure do occur, but most reactions will occur soon after the patient starts to take the medicine.)

2.3.4 The nature of the event should be considered when assessing the significance of the period of exposure, for example:

- 2.3.4.1 some events take a long time to develop (e.g. cancer);
- 2.3.4.2 some develop quickly (e.g. nausea and headache);
- 2.3.4.3 allergic reactions to first-time exposure to a drug generally take around 10 days to appear. On repeat exposure they may occur immediately.

2.4 Did the event occur after the commencement of some other medicine?

If the event began shortly after commencing another medicine, then two possibilities should be considered.

2.4.1 The new medicine may have caused the event.

2.4.2 There may have been an interaction between the two drugs and the interaction caused the event.

2.5 Did the event occur after the onset of some new illness?

If so, the event may be due to the new illness.

2.6 What is the response to withdrawal of the medicine (dechallenge)?

2.6.1 Did the patient recover?

2.6.2 Did the patient improve?

2.6.3 Was there no change?

2.6.4 Did the patient get worse?

2.6.5 Is the response to dechallenge unknown? If this is the case, then it should always be recorded as unknown.

If more than one medicine has been withdrawn, and if rechallenge is considered appropriate, it should be performed with only one medicine at a time.

2.7 What is the response to rechallenge?

Conditions for a positive rechallenge are:

2.7.1 the patient recovered on initial withdrawal;

2.7.2 the patient developed the same problem again when re-exposed to the same medicine alone, although it may be of different severity;

2.7.3 the patient recovered when the medicine was withdrawn once again;

2.7.4 it should be noted that it is not always safe to subject the patient to a rechallenge;

2.7.5 if the response to rechallenge is unknown, this should be recorded.

3. Categories of relationship

There are six standard categories of relationship between drug and event. These are the same as the causality categories in the WHO International Drug Monitoring Programme:

3.1 certain (or definite);

3.2 probable;

3.3 possible;

3.4 unlikely;

3.5 unclassified (or conditional);

3.6 unassessable (or unclassifiable).

4. Requirements for inclusion of an event in a specific category

4.1 Certain

4.1.1 The event is a specific clinical or laboratory phenomenon.

4.1.2 The time elapsed between the administration of the drug and the occurrence of the event is plausible. (*Requirement*: dates of drug administration and date of onset of the event must be known.)

4.1.3 The event cannot be explained by concomitant disease or any other drug or chemical. (Requirement: Details of other medicines taken must be known. The report must also state if there were no other medicines in use. If this is unknown, then doubt exists and the event cannot be included in this category.)

4.1.4 The patient recovered within a plausible length of time following withdrawal of the drug. (*Requirement*: The date of withdrawal of the drug and the time taken for recovery should be known. If these dates are unknown, then doubt exists and the event cannot be included in this category.)

4.1.5 The same event recurred following rechallenge with the same drug alone. (*Requirement*: The report must state the outcome of rechallenge. If this is unknown, then doubt exists and the event cannot be included in this category.)

4.2 Probable

4.2.1 The event is a specific clinical or laboratory phenomenon.

4.2.2 The time elapsed between the administration of the drug and the occurrence of the event is plausible. (The dates of drug administration and date of onset of the event must be known.)

4.2.3 The event cannot be explained by concurrent disease or any other drug or chemical. (Details of other medicines taken must be known. The report must also state if there were no other medicines in use. If this is unknown, then doubt exists and the event cannot be included in this category.)

4.2.4 The patient recovered within a plausible length of time following withdrawal of the drug. (The date of drug withdrawal and the time taken for recovery should be known.)

4.2.5 Rechallenge did not occur, or the result is unknown.

4.3 Possible

4.3.1 The time elapsed between the administration of the drug and the occurrence of the event is plausible. (The dates of drug administration and date of onset of the event must be known.)

4.3.2 The outcome of withdrawal of the suspect medicine is not known, and/or the medicine might have been continued and the final outcome is not known; and/or

4.3.3 there might be no information on withdrawal of the medicine; and/or

4.3.4 the event could be explained by concomitant disease or use of other drugs or chemicals; and/or

4.3.5 there might be no information on the presence or absence of other medicines.

4.3.6 *Deaths* cannot be coded as probable because there is no opportunity to see the effect of withdrawal of the drug. If there is a plausible time relationship, a death should be coded as possible.

4.3.7 In addition to deaths, there is a further group of events that do not fit the relationship assessment process and the coding can vary. Consider the following examples:

4.3.7.1 *Myocardial infarction*. Many patients recover from this event as part of the natural history of the disease and, with very few exceptions, recovery is not a response to withdrawal of a drug.

Hence the result of "dechallenge" is meaningless. This type of reaction may be coded as "possible".

4.3.7.2 *Stroke*. Some patients recover fully, some partially, some remain severely disabled and some die. All these outcomes are part of the natural history of the disease and, with very few exceptions, are unrelated to drug withdrawal. Again, the result of "dechallenge" is usually meaningless. This type of reaction may be coded as "possible".

4.3.7.3 *Acute anaphylaxis immediately following an injection*. Here there is an obvious direct relationship, but the usual parameters for establishing relationship, e.g. dechallenge do not apply. In this example, the best category for the relationship is "certain".

4.4 Unlikely

4.4.1 The event occurred with a duration to onset that makes a causal effect improbable with the drug being considered. (The pharmacology of the drug and nature of the event should be considered in arriving at this conclusion.); and/or

4.4.2 the event commenced before the first administration of the drug; and/or

4.4.3 the drug was withdrawn and this made no difference to the event when, clinically, recovery would be expected. (This would not apply for some serious events such as myocardial infarction, or events causing permanent damage.); and/or

4.4.4 it is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved.

4.5 Unclassified or conditional

These are reports with insufficient data to establish a relationship and more data are expected. This is a temporary repository, and the category for these events will be finalized when the new data become available.

4.6 Unassessable

4.6.1 An event has occurred in association with a drug, but there are insufficient data to make an assessment.

4.6.2 Some of the data may be contradictory or inconsistent.

4.6.3 Details of the report cannot be supplemented or verified.

5. Processes for establishing the relationship

The use of CemFlow ensures a methodical approach to relationship assessment. If this cannot be used because of a poor Internet connection, use of a coding sheet before data entry (referred to in section E.3.4) is very helpful (see Annex 6 for an example). The following should be recorded systematically.

5.1 Result of dechallenge

Select the most appropriate outcome:

5.1.1 event resolved;

5.1.2 resolving;

5.1.3 resolved with sequelae;

5.1.4 not resolved;

5.1.5 worse;

5.1.6 death;

5.1.7 unknown;

5.1.8 no dechallenge (medicine continued).

5.2 Result of rechallenge with the same medicine by itself

Select the most appropriate outcome:

5.2.1 recurrence of problem;

5.2.2 no recurrence;

5.2.3 unknown;

5.2.4 no rechallenge.

5.3 Outcome of the event

Select the most appropriate term:

5.3.1 resolved;

5.3.2 resolving (as at a recorded date);

5.3.3 not resolved;

5.3.4 worse;

5.3.5 patient died;

5.3.6 permanent disability;

5.3.7 unknown.

5.4 Clinical details

5.4.1 concomitant disease(s);

5.4.2 relevant patient history, e.g. liver disease or renal disease;

5.4.3 previous exposure to same medicine(s):

5.4.3.1 yes or no?

5.4.3.2 any reaction to previous exposure – yes or no?

5.4.3.3 if "yes", record the reaction term(s) for previous reaction(s).

5.5 Logic check

It is very easy to make mistakes in assigning a relationship. The final step should be a check on your logic. Some of the considerations are as follows:

5.5.1 you should not have a relationship of "certain" if there has been no rechallenge, or the outcome of rechallenge is unknown;

5.5.2 you should not have a relationship of "probable" if there has been no dechallenge or the result of dechallenge is unknown;

5.5.3 you should not have a relationship of "probable" if the outcome of the event is unknown;

5.5.4 you should not have a relationship of "probable" if there are other possible causes of the event.

5.6 Reactions and incidents

It is useful for analytical purposes to divide the events into two groups.

5.6.1 Those events with a relationship coding of definite, probable or possible can be aggregated and referred to as "reactions" because the event is likely to be related to the medicine(s).

5.6.2 Those events with a relationship coding of unlikely, can be referred to as "incidents" because they appear to be incidental to the use of the medicine.

5.6.3 The following equation simplifies the concept and is consistent with the definition of "events": *events = reactions + incidents*.

H. Signal identification

(*For spontaneous reporting or cohort event monitoring*)

1. Introduction

1.1 General approach

The identification of signals in the PvC's, or another database, of adverse events or suspected adverse reactions requires careful review of individual reports and events. Careful, informed, routine, systematic and standardized clinical review of the Centre's reports with the recording and appropriate collation of good data provides the quickest and most satisfying way of identifying previously unsuspected adverse reactions. Following through the whole process from relationship assessment, to signal identification, to signal strengthening, to communicating the findings is essential.

1.2 Definition of a signal

1.2.1 "*Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.*"

1.2.2 Alternatively, there are several events (or sometimes a single event) with a strong relationship ("certain" or "probable" and sometimes "possible") and there does not seem to be good evidence anywhere of it being recognized as a reaction.

1.2.3 There may be one or two case-reports in the literature, but this is insufficient as validation and the signal needs to be strengthened.

1.3 Reference sources on adverse reactions

1.3.1 *Martindale, The Complete Drug Reference* is probably the most reliable source.

1.3.2 *The Physicians Desk Reference (PDR)* is also useful. However, the entries are mainly data sheets provided by pharmaceutical companies and contain many references to possible reactions that are not validated and the information is often difficult to interpret.

1.3.3 *Micromedex online drug reference* is a reliable source of information.

1.3.4 If there is not good evidence of an event being recognized as an adverse reaction in two or more of the above-mentioned references, then, if warranted clinically, it should be investigated further as a possible signal.

2. Good data are essential

2.1 The data in the report(s) need to be of good quality if a signal of a new adverse reaction is to be considered.

2.2 There should be sufficient data to fully assess the relationship of the drug to the event. The strongest signals will have several reports with a "certain" or "probable" relationship. A signal may possibly be identified from one very good "certain" report. If there are no "certain" reports, at least three "probable" reports would be necessary for a signal.

2.3 The first reports with a "certain" or "probable" relationship are called "**index cases**".

2.4 Cases with a "possible" relationship can only provide supporting evidence. A group of unexpected deaths coded as "possible" forms an exception to this general rule and will need to be taken seriously.

2.5 Cases coded as "unclassified" or "unassessable" should not be considered in the investigation of a signal.

2.6 A group of "unlikely" reports may occasionally produce a signal of an unexpected reaction that was not recognized at the time of clinical assessment. However, they should not be included in the assessment of a signal for which there are reports with certain, probable or possible relationships because they are different and could mask the characteristics of the signal being investigated.

3. Selection criteria for events to investigate

3.1 There are good data.

3.2 The event is clinically relevant.

3.3 There have been several reports of the event that show a credible and strong relationship with the drug (certain or probable).

3.4 If validated, the event is of sufficient importance or interest to:

3.4.1 require regulatory action;

3.4.2 require advice to prescribers;

3.4.3 be of scientific importance.

4. Methods of signal identification

- clinical assessment of individual events
- clinical review of collated events
- record linkage
- automated signal detection.

4.1 Clinical assessment of individual events

4.1.1 Careful, routine, standardized clinical assessment of individual reports, as described in section G, with alertness to the possibility of a signal, offers the quickest method of identifying signals.

4.1.2 This approach should be taken during routine review of incoming reports.

4.1.2.1 During routine assessment of reports, if an assessor identifies an event and thinks that it could be a new type of adverse reaction, a search should be undertaken for records of other similar events to confirm the opinion.

4.1.2.2 First, the database should be checked for other similar reports or clinically related terms.

4.1.2.3 Then the adverse reaction should be checked in the reference sources (section 1.1.3).

4.1.2.4 If there is no reference to the occurrence of the event as an adverse reaction, proceed with its investigation.

4.2 Clinical review of collated events

4.2.1 Regular review

All the events in the database for the drug(s) of interest (or class of drugs) should be reviewed at regular intervals e.g. each month.

4.2.2 Clinical presentation

This is facilitated by collating (sorting) the events by means of a computer programme into a clinically orientated structure so that the overall clinical picture of events occurring with the drug or regimen can be viewed. This is

accomplished by sorting the event terms by the events dictionary codes (see section D.9.3).

4.2.3 Collating the events

4.2.3.1 By this stage, the individual events have been assessed, and each event should have had a term applied to it that is selected from the events dictionary. There is a dictionary code for each of these terms and this should be added to the database with the terms during data entry. Using CemFlow the application of the code is automated.

4.2.3.2 The dictionary terms are coded in such a way that clinically related events appear together when the events are sorted by code.

4.2.3.3 The events can then be printed out or seen on the computer monitor in a systematic clinical structure. Groups of related events are then seen clearly.

4.2.3.4 Example: for the investigation of cardiac failure as a possible signal, all possibly related events and conditions that might be associated with heart failure should be considered together. These would include cardiac failure aggravated, cardiac failure right, congestive heart failure, cardiac failure left, dyspnoea (assessed as of cardiac origin), peripheral oedema, jugular venous pressure increased, cardiomegaly, cardiomyopathy and heart valve disorders. The whole group of events should then be taken into consideration. (See Annex 8 for such an events collation.)

4.2.3.5 The events dictionary terms are coded in this clinically relevant way.

4.2.3.6 Annex 12 is a table which illustrates the collation of events in a clinical hierarchy and which also shows a signal.

- The table A12.1 shows eye events reported as being associated with COX-2 inhibitors from the IMMP in New Zealand.
- The listing demonstrates a signal of disturbance of vision including temporary blindness and visual field defect. All but one of the events listed under "Visual acuity" form part of the signal. There is one report that is "certain" and 12 "probable" reports. That makes a strong signal. There were four reports with a "possible" relationship which give

supporting evidence. There was also one report that is "unlikely" because there was another cause for the event. The reports under "Disturbance" are also likely to be related to this signal.

- This signal was published and is a good illustration of how to develop and validate a signal. (Coulter DM, Clark DWJ. Disturbance of vision by COX-2 inhibitors. *Expert Opinion on Drug Safety*, 2004, 3:607–614.)

4.2.4 Special reports

At the time of collation of all the events in the database into their clinical groups and sub-groups, using CemFlow, four special reports will be produced in addition to the general collation:

4.2.4.1 concomitant medicines.
These are listed in the report together with the events reported while they were in use;

4.2.4.2 pregnancy register;

4.2.4.3 lactation exposure;

4.2.4.4 dieds.
This perhaps unusual term is used to indicate that the patients died from whatever cause (and the causes will be listed) without any implication of an adverse effect of the medicine. This is necessary for event monitoring where the recording of events implies no cause and effect relationship. Death is an event and is recorded as 'died'. The use of the term, 'Deaths' might carry the implication that the death was caused by the monitored medicine or regimen and this is to be avoided because of the risk of creating a drug scare.

4.2.5 Special types of event

4.2.5.1 Deaths should be entered with the cause(s) given. The death event is termed 'died'. The causes of death should be collated within this category in the same way as events generally, using the dictionary code, so that they appear in clinically meaningful groupings. Any clinical patterns associated with death can then be seen easily. Rigorous validation procedures should then be applied to any suspicious patterns forming a signal (see section H1). An example of a collated listing of patients who died is shown in Annex 11.

4.2.5.2 Signals of interactions: All medicines used in association with the monitored medicines or regimen will be entered into the database and listed in a special report called "Concomitant medicines" at the time of the general collation. Each additional medicine is listed together with the events that occurred while it was being used, in order to facilitate visual signal identification of possible interactions. It is a record of events occurring with more than one medicine used. An example of a listing of Concomitant medicines is shown in Annex 13.

4.2.6 Review of events coded "unlikely"

4.2.6.1 There is always the possibility that unexpected reactions have been coded as "unlikely" and represent missed signals.

4.2.6.2 These events should be examined regularly for any unexpected patterns. If unexpected patterns emerge, they should be treated as signals and investigated as in section I.

4.3 Record linkage

4.3.1 Record linkage depends on the availability of a unique identifier for patients in the health system or in hospital records.

4.3.2 This same identifier must also be recorded with the patient details in the cohort database.

4.3.3 It can then be used as a tool to gather additional events data such as details of hospital admission.

4.3.4 The process involves matching the patient identifiers in the cohort with patient identifiers in any available databases or registers (e.g. register of deaths or hospital admissions).

4.3.5 When the patient records are linked in this way, it is possible to see, for example:

4.3.5.1 if the patient has died and the date and cause of death;

4.3.5.2 if the patient has been admitted to hospital and the diagnoses;

4.3.5.3 if the patient has been diagnosed with a disease of special interest for which a register has been created.

4.3.6 The results of the linkage are then reviewed and added to the records of events for the patients in the cohort. An unexpectedly high rate of a par-

ticular event (e.g. dystonic reactions or liver damage identified from hospital discharge diagnoses), may represent a signal.

4.4 Automated signal detection

4.4.1 Methods

4.4.4.1 The UMC regularly scans the WHO database for potential signals using its automated data mining program, the Bayesian Confidence Propagation Neural Network (BCPNN). This produces **Information Component** (IC) values for drug–event combinations. These can be plotted as graphs over time to examine any trend. A positive signal will have IC values that become more significant over time as more cases are included. This represents worldwide experience in the world's largest database.

4.4.4.2 The UMC will run this programme on request to investigate a particular drug–event combination of interest to the programme. This **data mining** technique is also available to users of CemFlow as one of the analytical tools.

4.4.4.3 **Proportional reporting ratios** (PRR). This is a method that uses software to measure the proportion of reports in the database with a particular drug–event combination and compares this proportion with that for the same event in the reports for all other drugs combined. If the PRR for a particular drug–event combination is significantly high, and it is not a recognized reaction, it may represent a signal.

4.4.2 Usefulness

4.4.2.1 Automated methods can strengthen a signal identified by clinical evaluation.

4.4.2.2 They may identify signals that were missed during assessment of the reports and later review.

4.4.2.3 The BCPNN runs on all reported events worldwide and there is therefore a greater chance of finding more reports of the suspect drug–event combination. It is performed routinely.

5. Comment

5.1 Identifying signals in "real time" by clinical evaluation during routine assessment and regular review of the events in the database for a drug, will find most signals earlier than automated methods will.

5.2 PRR methods are more reliable in large databases, but are still somewhat experimental and lack reliability.

5.3 All signals identified from statistical programmes (BCPNN or PRR) require subsequent clinical evaluation.

I. Strengthening the signal

1. General approach

Clinical evaluation of signals identified by BCPNN may also be thought of as "strengthening" the signal. Validating a signal is generally a process of gradual strengthening arising from new findings in pharmacovigilance or research. The process entails examining other available data and also examining one's own data in greater depth according to the following principles:

1.1 reviewing other experience;

1.2 searching for non-random patterns;

1.3 reviewing the pharmacology;

1.4 consulting one's expert safety review panel and other experts;

1.5 undertaking epidemiological studies;

1.6 communication and feedback.

2. Other experience

2.1 Are there other similar reports in the database? Look for **related clinical events** for the suspect drug and not simply a single event term. Also, look at related drugs in the same ATC classification grouping.

2.2 Search the worldwide database of suspected adverse reactions of the WHO Collaborating Centre (the UMC, available at: https://vigisearch.who-umc.org/).

2.3 Request the Information Component (IC) value for the drug–event combination from the WHO Collaborating Centre (the UMC). (This will indicate if the particular drug–event combination has been reported more often than would be expected and give a measure of the statistical significance.) This is available to users of VigiFlow or CemFlow as one of the analysis tools. The IC value for a drug–event combination can often be found in the combinations database provided to National Centres by the UMC.

2.4 Ask for information held by other National Centres through the Vigimed e-mail network coordinated by the UMC.

2.5 Search the literature for similar reports, using search tools such as PubMed or Micromedex.

2.6 Ask the pharmaceutical company if they have received similar reports and ask for details.

2.7 Were similar events identified in clinical trials? (Search the literature and/or ask the company for reports of clinical trials of the medicine.)

2.8 Were similar events identified in preclinical studies? (Ask the pharmaceutical company.)

2.9 Has this event, or have any similar events, been identified in post-marketing cohort event monitoring (prescription event monitoring or IMMP) studies?

3. Search for non-random patterns

Examination of data on a group of reports may show patterns that are not random and, in the absence of biases, non-random patterns suggest that the events may be related to the medicine.

3.1 Onset times

Does the range of onset times cluster around a particular period (e.g. 5 days or 3 weeks), or are the onset times scattered randomly over time? Compare the onset times of the events with those for the rest of the cohort using life-table or survival analysis.

3.2 Mean dose

Is the mean dose significantly higher in those who experienced the event being studied than in those in whom the event did not occur?

3.3 Mean age

Is the mean age of patients in whom the event occurred significantly different from that of those who did not experience the event?

3.4 Sex differences

When compared with the cohort, are the rates of the event in men and women significantly different? A drug effect could be one reason for this.

4. Comparison with control events

4.1 Should a group of events in the post-treatment group be suspected of signalling a reaction, the rate should be compared with the same event terms from the pre-treatment data. A higher rate of statistical significance for the suspect events would provide confirmatory evidence of a causal relationship with the monitored medicine(s).

4.2 The incidents (non-reactions) (see section G5.5.6) can be used as an internal control. If, for example, the suspect events showed different characteristics from the incidents, this would suggest a causal relationship with the monitored medicine(s).

5. Pharmacology

5.1 Is there a plausible pharmacological mechanism by which the medicine could cause the event?

5.2 Have other drugs in the same class caused a similar problem and has a mechanism been described for the related drug(s)?

5.3 Note that with a new medicine there may not be a known mechanism for a new adverse reaction. Sometimes the study of a previously unidentified adverse reaction brings to light new knowledge about the pharmacology of the medicine.

6. Investigative epidemiological studies

Investigative epidemiological studies may be needed if the event seems important. These studies may require collaboration with others who have expertise in this field. Such studies include:

6.1 cohort studies;

6.2 case–control studies;

6.3 record linkage studies;

6.4 population database studies.

7. Communication

Effective, well-presented communication of the signal to the various stakeholders will inform and give you feedback on its validity and its importance.

The following stakeholders can provide invaluable advice:

7.1 Expert Safety Review Panel and/or regulatory authority;

7.2 health practitioners;

7.3 the Uppsala Monitoring Centre;

7.4 the pharmaceutical company;

7.5 country ADR bulletin;

7.6 letter or report to a medical journal.

J. Identifying risk factors

1. Introduction

1.1 Definition

A risk factor is a characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction. Knowledge of risk factors provides a means of avoiding or minimizing the number of adverse reactions they relate to. Risk factors may be associated with:

1.1.1 the patient;

1.1.2 the medicine;

1.1.3 the environment.

1.2 Risk factors associated with the patient

1.2.1 age;

1.2.2 size: weight and height or body mass index (BMI);

1.2.3 genetic polymorphism (CYP 450 enzymes) (see Annex 15 for resource);

1.2.4 pregnancy;

1.2.5 concomitant illness (e.g. tuberculosis);

1.2.6 renal or liver damage.

1.3 Risk factors linked to the medicine

1.3.1 dose;

1.3.2 duration of therapy;

1.3.3 previous exposure (allergic-type reactions);

1.3.4 concomitant medicines.

1.4 Risk factors linked to the culture or environment

1.4.1 cigarette smoking and other tobacco use;

1.4.2 alcohol or other drugs;

1.4.3 diet (e.g. grapefruit juice);

1.4.4 traditional medicines.

2. Identification

2.1 Pharmacology

Knowledge of the pharmacodynamics and pharmacokinetics of a drug may allow certain adverse reactions to be predicted, but does not identify them.

2.2 Clinical trials

Risk factors for certain adverse reactions might be identified in clinical trials, but these trials are not designed to examine safety issues and the opportunity is limited because of small numbers of participants.

2.3 Clinical experience

Clinical experience might create the impression that certain characteristics are risk factors, but if rates are not measured, these impressions are unreliable.

2.4 Spontaneous reporting

2.4.1 Risk factors cannot be identified with certainty from spontaneous reporting because of the absence of rates. If a particular characteristic appears more frequently than expected in adverse reaction reports e.g. younger age group, it might be assumed that this is a risk factor, but such assumptions are unreliable. The predominance of younger patients might be due to the age distribution of the population being monitored.

2.4.2 Rates can be calculated using the defined daily dose (DDD), but these estimates suffer from the fact that spontaneous reporting is incomplete and the rates will be very low. Also there are often strong biases in spontaneous reporting which distort the findings. However, rates based on DDDs can be useful for comparing similar medicines given under similar conditions if every effort is made to identify possible confounders.

2.5 Cohort event monitoring

2.5.1 Measure the differences

With knowledge of the characteristics of the whole cohort it is possible to measure the differences between patients in whom adverse reactions occur and those in whom they do not and thus identify risk factors.

2.5.2 Relative risk

The simplest approach is to measure the rate of a characteristic in patients from the cohort who have experienced the adverse reaction under investigation, and compare it with the rate in patients in the cohort in whom the reaction did not occur. The relative risk (RR) can then be calculated by dividing the rate in those who did have the reaction by the rate in those who did not have the reaction.

Confidence intervals (CI) should be calculated in order to assess the statistical significance of any difference found. This method is subject to biases or confounders because of possible differences between the two groups, e.g. concomitant medicines or prescribing bias. These differences might be multiple e.g. concomitant disease plus cigarette smoking.

2.5.3 Multiple logistic regression

This is a powerful statistical method that will control for several characteristics in the one calculation and identify risk factors reliably. If you wish to employ this method it is best to consult a biostatistician.

2.5.4 Case–control studies

These can be undertaken to examine characteristics for which no data have been collected. As an example, abnormal renal function might be suspected as a risk factor. To investigate this, a sample of patients who have had the adverse reaction under investigation is selected together with a matching sample of patients in the cohort who did not have the adverse reaction. Renal function tests are then undertaken and the rates of abnormal function calculated for each group. The RR for the reaction group is then calculated. Confidence intervals for the RR will reveal whether any difference found is statistically significant and if abnormal renal function is a risk factor. (This is called a **"nested" case–control study**.) This type of study can be used to identify any influence of genetic polymorphism.

K. Analyses

A number of different analyses have been mentioned in this handbook. All but one or two can be undertaken by pharmacovigilance staff. CemFlow and VigiFlow have built-in analytical techniques. This section is mainly a listing in two categories of the analytical methods that are likely to be most helpful: data manipulation and statistical methods.

1. Data manipulation

1.1 Tabular

1.1.1 summary of reporting rates for males, females and totals;

1.1.2 age and sex profiles of the cohort;

1.1.3 patient numbers by region or site;

1.1.4 event profiles by clinical category;

1.1.5 listing of events by clinical category with sex, age, dose, duration to onset, relationship, and outcome. This tabulation gives a very good clinical picture of the events occurring in the cohort (see Annex 8);

1.1.6 comparison of event profiles pre-treatment and post-treatment;

1.1.7 rates of important events pre-treatment and post-treatment with relative risks;

1.1.8 table of the most frequent post-treatment events with numbers and rates and outcome (treatment withdrawn, deaths);

1.1.9 case-report listing (lists all events for each case-report);

1.1.10 reasons for non-adherence or withdrawal of treatment.

1.2 Graphic

Some of the above information (e.g. the profiles) can be presented helpfully as bar graph (see Annex 9).

2. Statistical analyses

Simple statistical analyses will provide most of the analytical data needed.

2.1 The calculation of risk

The rate (or risk) can be calculated for any event or group of events.

2.2 Attributable risk

The difference between the absolute risk (rate in the treated group) and the rate when the cohort was not exposed to the medicines (the control period) provides the attributable risk, which is the increased risk associated with exposure to the monitored medicine(s). This does not apply to events of late onset in the context of the protocol outlined in this handbook.

2.3 Relative risk (RR) with confidence intervals (CI) (see section J2.5.2).

2.4 t-test for the comparison of means.

2.5 Life-table analysis (survival analysis)

For the event being studied, this type of analysis can identify the duration to onset for every patient who experienced the event and calculates the rates for patients in whom the event has occurred (or the survivors) at specified points in time. This can be used to measure the range of onset times of any event and to assess if there is a non-random relationship with the drug (see section I3).

2.6 Multiple logistic regression

This is used mainly for determining risk factors. This type of analysis should be undertaken only by a biostatistician.

L. Differences between spontaneous reporting and CEM

1. Cohort event monitoring

1.1 Advantages

1.1.1 The ability to produce rates.

1.1.2 The ability to produce a near complete profile of the adverse events and/or adverse reactions for the medicines of interest.

1.1.3 Very effective in identifying signals at an early stage.

1.1.4 The ability to characterize reactions in terms of age, sex and duration to onset, and dose, and thus produce risk factors. Other relevant data may be collected such as on weight, comorbidity or region in order to provide the opportunity for determining other risk factors. (These calculations are dependent on having rates.).

1.1.5 The ability to make accurate comparisons between medicines.

1.1.6 The ability to establish a pregnancy register and identify problems with pregnancy and common congenital abnormalities.

1.1.7 The method, using routine follow-up, can detect reduced or failed therapeutic effect and thus raise suspicion of inaccurate diagnosis of disease, poor prescribing, inadequate adherence to treatment, emerging resistance or poor quality or counterfeit medicines.

1.1.8 The ability to record and examine details of all deaths and provide rates of death.

1.1.9 The ability to produce rapid results in a defined population.

1.1.10 This method collects comprehensive and near-complete data that will provide for the special needs of the HIV programme, including effects of ART in pregnancy, specific toxicities and safety in children.

1.1.11 Because the method looks intensively at new drugs of great interest in a specific area of need, and provides clinically significant results rapidly, it stimulates interest in drug safety in general.

1.1.12 The method provides sound evidence with which to deal with any drug scares.

1.2 Disadvantages

1.2.1 The method is more labour intensive and more costly than spontaneous reporting.

1.2.2 It will be new to health professionals and PvCs and training in its use will be necessary.

2. Spontaneous reporting

2.1 Advantages

2.1.1 It is administratively simpler and less labour intensive than CEM.

2.1.2 It is less costly than CEM.

2.1.3 It is the most common method of pharmacovigilance used.

2.1.4 PvCs and health professionals are more likely to be familiar with this method.

2.2.5 It provides safety surveillance throughout the marketed life of all medicines.

2.2 Disadvantages

2.2.1 The data collected by this method are incomplete. In developed countries less than 5% of reactions are reported. A report from the WHO filariasis programme suggests that compliance with reporting in a public health programme is likely to be much lower than this, leaving many unanswered questions.

2.2.2 Reliable rates cannot be calculated and so risk cannot be measured and risk factors cannot be established with confidence.

2.2.3 There are strong biases in reporting.

2.2.4 Deaths are poorly reported.

2.2.5 Special studies will need to be set up to obtain accurate information on areas of particular interest e.g. pregnancy, children and specific events of concern. These special studies add to the cost and in turn reduce the cost advantage of spontaneous reporting.

M. Organization

1. Legislation

1.1 Legal authorization

Spontaneous reporting and CEM programmes form the data collection arms of pharmacovigilance activities. The collection of data required for spontaneous reporting and CEM programmes should be authorized or required by law. Pharmacovigilance is non-interventional and will not create any physical risk to patients. Spontaneous reporting and CEM programmes are not clinical trials. They are methods of public health surveillance requiring the collection of certain types of data in the public interest. Public health surveillance is frequently conducted under specific laws authorizing or requiring the collection of certain types of data. In some countries, reporting on the risks associated with medicines is mandatory. All medicines are subject to spontaneous reporting. Selected new medicines that are to be used widely and are of public health importance should be subject to CEM where possible. ART is a typical example. Leaders in the field of pharmacovigilance in each country should advocate the legal endorsement or requirement for pharmacovigilance activities of both types.

1.2 Conditional registration

The legal status of data collection for pharmacovigilance can be reinforced by further legal requirements or regulations that require specified new medicines of public health importance to be subject to CEM before full registration is granted. Conditional registration can be offered until the outcome of a CEM study is known, at which time full registration can be approved or declined on the grounds of safety.

1.3 Regulation of professional standards

In many countries the standards of health professionals are maintained and improved by compulsory continuing medical education (CME). It is justifiable for CME credits to be given for pharmacovigilance activities. Sending spontaneous reports or CEM questionnaires to the PvC displays, on the part of the health professional concerned, professional responsibility, good medical

practice and involvement in activities that improve the standard of patient care and safety. In addition, the activity provides a learning process both through the completion of the forms, which requires thinking about safety issues, and from the feedback received from the PvC. Professional associations should be encouraged to include spontaneous reporting and CEM in their approved CME activities.

2. Ethical issues

2.1 Introduction

2.1.1 Ethical principles must be applied consistently to all types of pharmacovigilance methods. The ethics of collecting data for CEM, in particular, have special features since it is a methodology which requires the collection of detailed personal data and sometimes stores these data for indefinite periods. There may often be a need for follow-up at a later date for the further study of any safety concerns identified, at which time there will be a need to conduct investigations such as a more detailed cohort study, nested case–control studies, comparative safety studies, investigations in a subgroup (e.g. in children) or even a full clinical trial.

2.1.2 Before starting the process of commencing a CEM programme, there must be open discussions with all the stakeholders including patients. Most importantly, early in the planning stage, endorsement must be sought from the health ministry without whose support little will be achieved. Open communication must follow with professional organizations, all health providers, the pharmaceutical industry, the general public, community leaders and the media.

2.1.3 Because it is essential to record personal identifiers, the security, privacy and confidentiality of personal data need to be strenuously maintained. Pharmacovigilance will not work properly if personal identifiers are not available. With both spontaneous reporting and CEM programmes, the ability to follow up specific patients on important outcomes is essential. With CEM, which can measure risk (incidence) and identify risk factors, it is essential that duplicate entries are avoided so that the accuracy of these findings is not compromised by an inflated denominator, and this can only be done if patients can be correctly identified. This necessity for recording patient identifiers therefore imposes strict conditions on maintaining data security. These are outlined as follows.

2.2 Prerequisites to collecting patient data

2.2.1 It is important to seek the approval of the highest appropriate authority in the country. This may be the ministry of health or the regulatory authority.

2.2.2 It is important to declare publicly what data are being collected and why.

2.2.3 The stated purposes should be broad enough to include:

2.2.3.1 long-term follow-up looking for signals of delayed reactions;

2.2.3.2 use of the data to enable follow-up investigations such as nested case–control studies to be undertaken to identify risk factors. It is not always possible to predict what additional studies might be needed for the investigation of safety issues that are identified during monitoring, and so approval should be sought for storage of the data to enable further investigations if necessary;

2.2.3.3 follow-up studies required to validate signals;

2.2.3.4 comparative studies with new ARVs or regimens.

2.2.4 Security and confidentiality arrangements should be publicized and should conform with any national legislative requirements.

2.3 Training of staff

2.3.1 Staff members responsible for pharmacovigilance need to be trained in the strict maintenance of security and confidentiality.

2.3.2 They should be required to sign a document saying that they understand the privacy issues and after appropriate instruction, agree to maintain security and confidentiality.

2.4 Security issues

2.4.1 Data that might identify patients should be stored on computers with no Internet link. This prevents access by hackers. This precaution will be impractical and unnecessary for those using VigiFlow or CemFlow.

2.4.2 Access to a computer that has data on it that might identify patients should be controlled by password.

2.4.3 Password access should be given only to those people involved in the particular pharmacovigilance activity.

2.4.4 Access to the premises should be security controlled.

2.5 Use of data

2.5.1 The data collected should be used only for the purposes declared.

2.5.2 Personal identifiable data should not be given to any other parties including pharmaceutical companies, government or ministry officials, agencies and research groups. This includes personal details of patients or reporters. Only anonymized data may be shared.

2.6 Confidentiality

2.6.1 No published data, including reports, should contain any information that could identify patients.

2.6.2 Staff should not take any identifiable data home or to places outside the PvC.

2.6.3 Staff should not discuss information outside the monitoring centre that could lead to the identification of any patient.

2.7 Informed consent

2.7.1 If pharmacovigilance activities, spontaneous reporting and CEM are authorized or required by law, informed consent from individual patients is not required for the collection of data required for safety monitoring. However all the privacy conditions outlined above should be strictly observed.

2.7.2 Programme managers should avoid attempting to obtain individual informed consent if at all possible because it will be time-consuming to try to explain the concepts of pharmacovigilance (which will often be culturally strange) to each patient, will increase complexity and add to the cost, and could potentially compromise the validity of the results if many patients refuse to be enrolled. A CEM programme is **not** a clinical trial or research study and does not interfere with treatment in any way. It is simply a process of observation data collection in the interests of public health.

2.7.3 An alternative to obtaining informed consent from individual patients is to provide information publicly (see section D.3) and to give patients leaflets which they can study, or have explained to them, away from the pressure of the clinics, and which provide them with contact details for the health facility and PvC so that they can object to having their data stored if this is their decision. Their data can then not be entered or if they have already been entered, they will be deleted. This is called the "**opt out principle**" which operates in

a number of countries and, if needed, is much more practical than individual informed consent.

3. Structure

3.1 Pharmacovigilance centre

The development of a PvC and its relationship to public health programmes is discussed fully in the following WHO publications:

3.1.1 *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre.*

3.1.2 *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool.*

3.2 Centre staff

3.2.1 Capacity

It is essential that the PvC has sufficient additional capacity to run CEM studies. For two parallel CEM studies (i.e. a comparator study of two medicines or regimens) to be undertaken, it is suggested that the following personnel would be necessary:

3.2.2 Clinical supervisor/reviewer

A full-time clinical supervisor who would be in charge of the CEM activities. This person would:

3.2.2.1 review the events reported on the questionnaires and would undertake relationship assessment, arrange follow-up of reports as required, liaise with the HIV programme manager, request appropriate data analysis, report regularly to the Expert Safety Review Panel in conjunction with the HIV programme manager and consult them about any concerns arising from the data, any reports of serious events and any signals of new adverse reactions;

3.2.2.2 be responsible for communication in collaboration with the HIV/AIDS programme manager. This would involve promotional activities as outlined in section D3.

3.2.2.3 be responsible for the training of Centre and peripheral staff.

3.2.3 Data manager

A full-time data manager would maintain the database, be responsible for quality assurance, ensure security and confidentiality of data, be responsible

for collating the data at an agreed frequency and for producing reports as required, ensure the supply of questionnaires to all health facilities, train and supervise the data processors and generally assist the clinical supervisor.

3.2.4 Data processor(s)

One or two full-time data processors employed for the duration of the monitoring programme. They would be responsible for data entry and certain other tasks under the supervision of the data manager.

3.3 Field staff for CEM

3.3.1 Field coordinator

Field staff will be under the supervision of a person with the role of field coordinator who will be responsible to the HIV programme manager and the clinical supervisor of the CEM programme. A simple chain of responsibility will need to be established (Figure 1).

3.3.2 A CEM focal person

A CEM focal person will need to be appointed to each sentinel site to be responsible for the following:

3.3.2.1 to ensure the collection of the data required for the CEM programme using whatever method is agreed upon for the HIV clinic at that site (see D5.7.3);

3.3.2.2 to ensure delivery and collection of completed questionnaires;

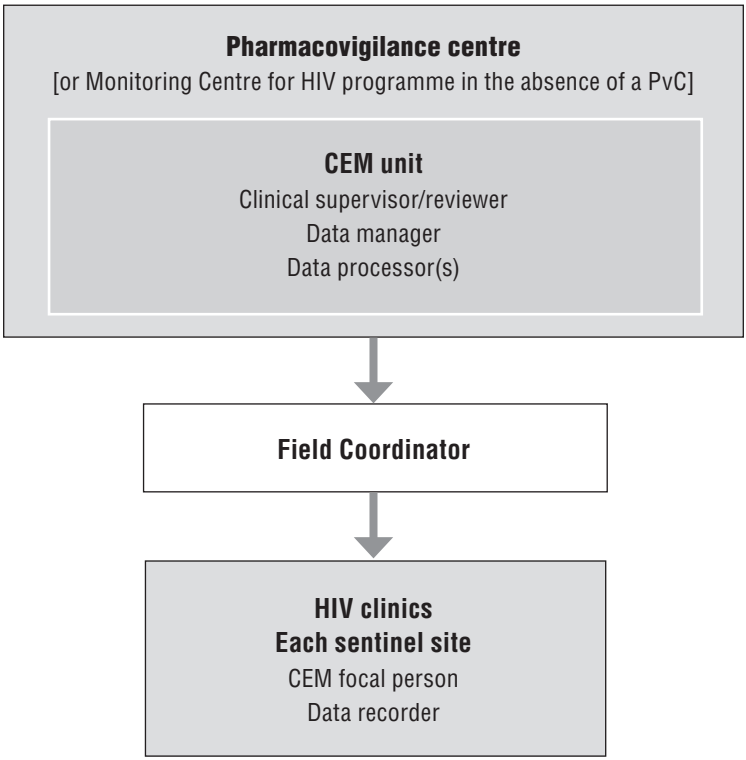
3.3.2.3 to maintain a local register of patients included in the CEM activity, to note appointments made for follow-up at the HIV clinic and, in liaison with staff at the HIV clinic, to help ensure follow-up of patients who miss their return appointment;

3.3.2.4 to maintain a register of pregnant women on ART and to note their return appointment times. To ensure follow-up of pregnant women if they miss their follow-up visit to the HIV clinic. They will also need to liaise with antenatal clinics and birthing facilities to collect follow-up data on the pregnancy and the outcome of childbirth;

3.3.2.5 to ensure follow-up of all deaths in order to find out the history of events leading to death, the cause of death and the date of death.

FIGURE 1

Suggested chain of responsibilities for CEM



3.3.3 Data recorder

A data recorder will need to be appointed to each sentinel site if the clinic staff cannot cope with this work. The data recorder will be responsible to the CEM focal person and will use the methodology agreed locally for completing the questionnaires.

3.3.4 Support

The field coordinator will be available to facilitate the work of the CEM focal person and data recorder at the sentinel sites. This may include soliciting the help and coordination of the staff at the PvC, HIV programme personnel, antenatal, paediatric and birthing units.

N. Communication

Good communication is imperative at all times and its importance has been highlighted throughout this manual. Some basic principles are described in Annex 14. As described in this handbook, essential aspects of communication embrace two main objectives:

- promotion or advocacy of the methodology;
- sharing the results.

Communication is a two-way process, which means the Pharmacovigilance (or Monitoring Centre) should listen to and carefully consider the opinions of others. Much can be learnt and much goodwill can be created from this process even if you cannot accept or implement all the suggestions that are made. The following groups need to be included in the communication process:

- patients, support persons, including HIV support groups and the wider community;
- all players involved in the supply and therapeutic management of HIV disease;
- those with regulatory and public health responsibilities;
- the appropriate government officials;
- the appropriate academic institutions and departments;
- relevant professional organizations including the opinion leaders and practitioners;
- international: WHO, including Headquarters, regional offices and the UMC;
- the media;
- staff of the PvC, the Expert Safety Review Panel and others involved in the activities of monitoring.

See the following sections for references where communication is referred to specifically: D3; D7; I6; M2.2.2.2.

See also Annex 15 for a list of useful web sites, published resources and expert resource personnel where information and advice can be sought.

0. Annexes

These are listed in order to which they are referred in the text.

1. Ghanaian reporting form for ARV medicines
2. Power and sample size analysis for statistical comparison of an event in two cohorts
3. Abbreviations for ARV medicines and regimens for ART
4. CEM monitoring questionnaires 1, 2 and 3
5. Patient ID card – suggested format
6. Coding sheet for reviewing of events before data entry
7. Major clinical categories in CEM events dictionary
8. Example of events collation
9. Comparative events profiles
10. Pregnancy questionnaires A, B and C
11. Table of collation of deaths (as events)
12. Table of eye events with COX-2 inhibitors illustrating a signal
13. Table of concomitant drug events associated with celecoxib
14. Advice on communication
15. Resources
16. Suggested standard operating procedures for CEM.

Annex 1. Ghanaian reporting form for ARV medicines

IN STRICT CONFIDENCE

Adverse Event Form for Anti-Retroviral Medicines

IN STRICT CONFIDENCE

Please complete as much as possible, regardless of any missing details

PATIENT DETAILS

Folder Number: Patient initials: Sex: [M] [F]

Residential Address: Town/City:

District: Region:

Date of birth: … /… /… Age: …… years …… months Weight (kg): ……

Type of Treatment ☐ HAART ☐ PMTCT ☐ PEP

DRUG DETAILS

	Drug I	**Drug 2**	**Drug 3**	**Drug 4**
1st Line Drugs	Combivir/Nevirapine	Combivir/Efavirenz	Stavudine/Lamivudine/ Nevirapine	Stavudine/Lamivudine/ Efavirenz
	Dose:	Dose:	Dose:	Dose:
	Date started: …/…/…	Date started: …/…/…	Date started: …/…/…	Date started: …/…/…
2nd Line Drugs	Abacavir/ Didanosine/ Nelfinavir	Abacavir/ Didanosine/ Kaletra		
	Dose:	Dose:		
	Date started: …/…/…	Date started: …/…/…		
CONCOMITANT DRUG	Co-trimoxazole prophylaxis Dose:	Drug: Dose:	Drug: Dose:	Drug: Dose:
	Date started: …/…/…	Date started: …/…/…	Date started: …/…/…	Date started: …/…/…

DETAILS OF ADVERSE EVENT

Date event started:: …/…/… Date event stopped: …/…/…

Adverse reaction observed (please tick all that apply)

☐ Mouth sores ☐ Abdominal pains ☐ Vomiting ☐ Nausea ☐ Itching ☐ Skin rashes ☐ Diarrhoea
☐ Headache ☐ Dizziness ☐ Insomnia ☐ Dark-coloured urine ☐ Other (please specify): ……

Description of event (*continue on back page if necessary*):

Treatment or action taken (*continue on back page if necessary*):

Outcome (*please tick all that apply*)

☐ Change of therapy ☐ Recovered without change of therapy ☐ Death
☐ Required / prolonged hospitalization ☐ Ongoing ☐ Other outcome (please specify)

REPORTER DETAILS

Profession: ☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Other

Last Name: …… Other Name(s): …… Title: ……

Address: …… Tel No. …… Email: ……

Signature: …… Date:……

Please return this form to: YOUR ART FOCAL PERSON:

Forms MAY also be sent to The Centre for Pharmacovigilance, CTCPT, UGMS, 2nd Floor Medical Block Building, Korle-Bu Teaching Hospital, Box 4236, Accra, Ghana Tel: 021-675885/668219; Fax: 668219

Annex 2. Power and sample size analysis for statistical comparison of an event in two cohorts

TABLE A2.1

With an incidence of the event of 0.1% in one cohort

Significance level[a]	Power[b]	Incidence of ADE in one therapy (percentage)	RR	Sample size (each group)
0.05	0.80	0.10	2.0	25 476
0.01	0.80	0.10	2.0	36 961
0.05	0.80	0.10	3.0	8 805
0.01	0.80	0.10	3.0	12 636
0.05	0.80	0.10	4.0	4 993
0.01	0.80	0.10	4.0	7 123
0.05	0.80	0.10	5.0	3 416
0.01	0.80	0.10	5.0	4 853
0.05	0.80	0.10	6.0	2 573
0.01	0.80	0.10	6.0	3 647
0.05	0.65	0.10	6.11	1 913

[a] Significance level or α, is the type I error rate, which is the probability of falsely rejecting the null hypothesis that there was no association (in other words, RR = 1) between the event of interest and the exposure therapy.

[b] Power, is the probability that we reject the null hypothesis correctly.

Notes: With a sample of about 2000 patients on each therapy, the power to identify a difference in ADE rate between the two therapies would be only about 65%, even with a RR of 6.0 and 95% confidence interval.

TABLE A2.2

With an incidence of the event of 1.0% in one cohort

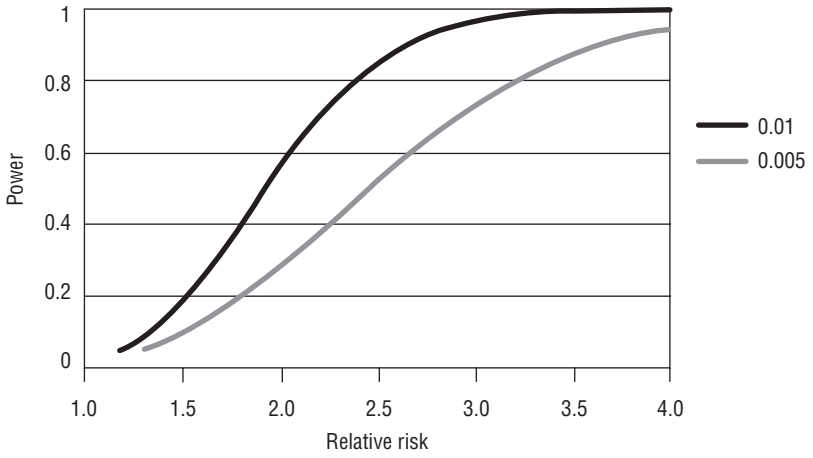
Significance level[a]	Power[b]	Incidence of ADE in one therapy (percentage)	RR	Sample size (each group)
0.05	0.81	1.0	2.40	1 500
0.05	0.85	1.0	2.50	1 500
0.05	0.89	1.0	2.60	1 500
0.05	0.91	1.0	2.70	1 500
0.05	0.94	1.0	2.80	1 500
0.05	0.80	1.0	1.90	3 000
0.05	0.84	1.0	1.95	3 000
0.05	0.87	1.0	2.00	3 000
0.05	0.90	1.0	2.05	3 000
0.05	0.92	1.0	2.10	3 000
0.05	0.81	1.0	1.67	5 000
0.05	0.84	1.0	1.70	5 000
0.05	0.86	1.0	1.73	5 000
0.05	0.89	1.0	1.76	5 000
0.05	0.91	1.0	1.80	5 000
0.05	0.81	1.0	1.45	10 000
0.05	0.84	1.0	1.47	10 000
0.05	0.86	1.0	1.49	10 000
0.05	0.90	1.0	1.52	10 000
0.05	0.92	1.0	1.54	10 000

[a] Significance level or α, is the type 1 error rate, which is the probability of falsely rejecting the null hypothesis that there was no association (in other words, RR = 1) between the event of interest and the exposure therapy.

[b] Power, is the probability that we reject the null hypothesis correctly.

FIGURE 1

Power curve of a sample size of 1500 (in each group) at incidence rates of 1.0% and 0.5% (P_0) in the control group



Notes: With a sample of about 1500 on each therapy, the power to identify a significant difference in ADE rate between the two therapies would be about 81%, if the RR is 2.40 and there is a confidence of 95% (the ADE incidence rate, P_0, is assumed to be 1.0%).

If P_0 is 0.5%, the RR has to be more than 3.20 to reach a power of about 80% with the same sample size, as is shown in the graph above.

Tables prepared by Dr Lifeng Zhou, NZ Pharmacovigilance Centre, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

Annex 3. Abbreviations for ARV medicines and regimens for ART

TABLE 1

Abbreviations for ARV medicines

/r	low dose ritonavir
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
AZT	zidovudine
D4t	stavudine
ddI	didanosine
EFV	efavirenz
FPV	fos-amprenavir
FTC	emtricitabine
IDV	indinavir
INH	isoniazid (TB)
LPV	lopinavir
NFV	nelfinavir
NVP	nevirapine
RBV	ribavirin
RTV	ritonavir
SQV	saquinavir
TDF	tenofovir
ZDV	zidovudine

TABLE 2

WHO recommended ART regimens

Adult 1st line regimens	
1 a(30)	d4t(30)-3TC-NVP
1b(30)	d4t(30)-3TC-EFV
1c	AZT-3TC-NVP
Id	AZT-3TC-EFV
Adult 2nd line regimens	
2a(250)	ABC-dd I (250)-LPV/r
2a(400)	ABC-dd I (400)-LPV/r
2b(250)	ABC-ddI(250)-SQVIr
2b(400)	ABC-ddI(400)-SQV/r
2c(250)	TDF-ddI(250)-LPV/r
2c(400)	TDF-dd I (400)-LPV/r
2d(250)	TDF-ddI(250)-SQV/r
2d(400)	TDF-ddI(400)-SQV/r
Child 1st line regimens	
4a	d4T-3TC-NVP
4b	d4T-3TC-EFV
4c	AZT-3TC-NVP
4d	AZT-3TC-EFV
Child 2nd line regimens	
5a	ABC-ddI-LPV/r
5b	ABC-ddI-NFV
5c	ABC-ddI-SQV/r

Annex 4. CEM Monitoring questionnaires

LOGO

Antiretroviral therapy: Cohort Event Monitoring

Baseline questionnaire

Unique number: .....

District: ..... Health unit: ..... Clinician/Team: .....

A. PATIENT DETAILS Patient Clinic

Patient ID number: .....

First name: ..... Family name: .....

Date of birth (dob): ...../...../..... (dd/mm/yy) *or if dob unknown*, age: ..... (years)

Sex: ☐ Male ☐ Female Weight (kg): ..... Height (cm): .....

Address: .....

If address not specific, nearest reliable contact: .....

Patient (or family member) mobile (cell) phone or telephone number: .....

B. HIV stage at this screening**:** .....

C. CURRENT MEDICINES

Medicine	Indication

D. LABORATORY TESTS *(blank row is for other tests)*

Test	Date (dd/mm/yy)	Result	Test	Date	Result
CD4 count			Cholesterol		
Viral load			Triglyceride		
ALT			Glucose		
Lymphocyte count			Total WC count		
Hb			Urine albumin		

E. PAST DISEASES OF IMPORTANCE AND ANY CURRENT CONDITIONS

Past diseases and current conditions	Year began	Year ended (tick if current)

Continue on other side of form if necessary

F. PREGNANT?: ☐ No ☐ Uncertain ☐ Yes

If yes, specify: ☐ 1st ☐ 2nd ☐ 3rd trimester.

PLEASE GIVE THIS FORM TO CEM FOCAL PERSON:

Focal Person: Name: ..... Phone: .....

LOGO

Cohort Event Monitoring Antiretroviral Therapy

Treatment Initiation

Patient CEM ID .....

Interview date dd / mm / yy

PATIENT DETAILS

Patient initials	**Date of birth** dd / mm / yy	**Age**	**Sex** male ☐ female ☐

TREATMENT PROVIDER

Monitoring site ..... **Clinician** ..... **Patient file number** .....

Interview site Health centre ☐ Hospital clinic ☐ Phone interview ☐ Home visit ☐

MEDICAL DETAILS

Weight (kg) .....
Height (cm) .....
WHO HIV clinical stage 1 ☐ 2 ☐ 3 ☐ 4 ☐
Indication for antiretroviral therapy Treatment of HIV ☐ Prevention of mother to child transmission ☐ Both ☐
Pregnant No ☐ Uncertain ☐ Yes ☐
➔ Estimated current gestation (months) .....
Breastfeeding an infant Yes ☐ No ☐

Pre-Existing and Past Medical Conditions EXCLUDE all medical conditions that began in the PAST 30 DAYS as these will be recorded below	**Date of onset**	**Date resolved**	**Continues**
			☐
			☐
			☐

EVENTS INCLUDE all NEW EVENTS or CHANGES in pre-existing conditions that BEGAN in the PAST 30 DAYS

NEW EVENTS in the PAST 30 DAYS	**Date of onset**	**Date recovered**	**Outcome[a]**	**Severity[b]**	**Seriousness[c]**

OUTCOME[a]
R Recovered
G Recovering
S Recovered with sequelae
N Not recovered
U Unknown

SEVERITY[b]
1 Mild
2 Moderate
3 Severe

SERIOUSNESS[c]
N Not serious
H Hospitalization (caused or prolonged)
P Permanent disability
C Congenital abnormality
L Life threatening

LABORATORY TESTS INCLUDE laboratory tests performed at any time during the PAST 30 DAYS

Test	**Date**	**Result (units)**	**Test**	**Date**	**Result (units)**

MEDICINES taken in the PAST 30 DAYS

Medicines and traditional medicines taken at any time in the PAST 30 DAYS	**Indication**	**Dosage**	**Frequency**	**Route**	**Start date**	**Stop date**	**Continues**
							☐
							☐
							☐

MEDICINES PRESCRIBED at this visit

ARV medicines	**Batch number**	**Dosage**	**Frequency**	**Start date**	**Quantity supplied**

Other medicines	**Indication**	**Dosage**	**Frequency**	**Route**	**Start date**	**Quantity supplied**

Focal person ..... **Phone** ..... **Date of next appointment** dd / mm / yy

Guidelines for completion of TREATMENT INITIATION FORM

The TREATMENT INITIATION FORM is completed during the consultation at which the patient is prescribed antiretroviral medicines for the first time. Completion of the treatment initiation form is all that is required to enrol a patient into the Cohort Event Monitoring programme.

Patient participation: It is important that monitoring begins at the commencement of therapy. Patients may be enrolled if they are beginning treatment with the monitored medicine(s) for the first time (i.e. treatment naïve) or if their ART regimen is being changed to include the monitored medicine(s). Women who have previously been exposed to ART for Prevention of mother to child transmission (PMTCT) may also be included in the cohort (regardless of current indication for ART).

Patients should be informed about the purpose of the monitoring programme and their agreement to participate should be sought prior to enrolment. Patients who are unwilling to participate should not be enrolled in the monitoring programme.

Patient CEM ID: The Patient CEM ID is the number used by the CEM programme to identify the patient. This number should be recorded on the treatment initiation form and on each subsequent treatment review form.

Tick boxes (☐): Please mark boxes with a tick ☑ where appropriate.

TREATMENT PROVIDER

Patient file number: Record the number you use to identify the patient at your clinic.

MEDICAL DETAILS

Weight and height: Record the patient's current weight (kg) and height (cm).

Indication for ART: Indicate whether ART is to be used for the **Treatment** of the patient's HIV infection or for the **Prevention of mother to child transmission**, or for **Both** reasons.

Pregnant: Indicate whether the patient is pregnant, not pregnant, or uncertain. If pregnant, record the current gestation in months.

PRE-EXISTING and PAST MEDICAL CONDITIONS: In this section, record all health conditions currently or previously experienced by the patient, EXCEPT for those that started in the past 30 days. Record the date (or approximate date) of onset of each condition; if the condition is ongoing tick the '**Continues**' box ☑ or if the condition has resolved record the date (or approximate date) in the '**Date resolved**' column.

EVENTS

NEW EVENTS in the PAST 30 DAYS: Record any NEW health events that STARTED IN THE PAST 30 DAYS (i.e. the 30 days prior to treatment initiation). Events to record include:

- all **new health events**
- any **deterioration or improvement in pre-existing conditions**
- **pregnancy-related conditions** including:
  - **complications** (e.g. gestational diabetes, pregnancy induced hypertension, preeclampsia, threatened miscarriage)
  - **type of delivery** (e.g. normal delivery, caesarean section)
  - **pregnancy outcome** (e.g. miscarriage, abortion, stillbirth, live infant, multiple birth)

LABORATORY TESTS

Tests and results: Record the results (including *units*) of any laboratory tests performed in the PAST 30 DAYS.

MEDICINES taken in PAST 30 DAYS

Medicines and traditional medicines taken at any time in the PAST 30 DAYS: Record the details of any prescription or over-the counter medicines and any traditional medicines, herbal remedies or health supplements taken at any time during the past 30 days. Include the units in the '**Dosage**' column. If a medicine is given as a fixed dose combination (FDC), either as a co-formulation or in a co-blister pack, record the number of dosage forms (DF) given.

MEDICINES PRESCRIBED at this visit

ARV medicines and other medicines: Record the details of all new medicines prescribed at this interview. ART medicines may be recorded either as individual medicines or as FDCs. Standard ART abbreviations may be used.

Quantity supplied: Please indicate the number of days supply or the number of tablets provided (or the volume for a suspension), including the units (days, tablets or ml).

LOGO

Cohort Event Monitoring Antiretroviral Therapy
Treatment Review

Patient CEM ID .....

Mother's CEM ID ..... (for INFANTS).

Interview date dd / mm / yy

PATIENT DETAILS

Patient initials	**Date of birth** dd / mm / yy	**Age**	**Sex** male ☐ female ☐

TREATMENT PROVIDER

Monitoring site ..... **Clinician** ..... **Patient file number** .....

Interview site Health centre ☐ Hospital clinic ☐ Phone interview ☐ Home visit ☐

MEDICAL DETAILS

Weight (kg) .....
WHO HIV clinical stage 1 ☐ 2 ☐ 3 ☐ 4 ☐
Indication for antiretroviral therapy Treatment of HIV ☐
Pregnant No ☐ Uncertain ☐ Yes ☐
Breastfeeding an infant Yes ☐ No ☐

Height (cm) .....
***or* INFANTS: HIV status** Negative ☐ Positive ☐ Unknown ☐
Prevention of mother to child transmission ☐ Both ☐
➔ Estimated current gestation (months) .....

EVENTS Record all NEW EVENTS or CHANGES in pre-existing conditions since last interview

New events since last interview	Date of onset	Date resolved	Outcome[a]	Severity[b]	Seriousness[c]	Rechallenge[d]

OUTCOME[a]
R Recovered
G Recovering
S Recovered with sequelae
N Not recovered
D Died
U Unknown

SEVERITY[b]
1 Mild
2 Moderate
3 Severe
C Congenital abnormality
L Life threatening
D Death

SERIOUSNESS[c]
N Not serious
H Hospitalization (caused or prolonged)
P Permanent disability

RECHALLENGE[d]
1 No rechallenge
2 Recurrence of event
3 No recurrence
4 Result unknown

LABORATORY TESTS Record all laboratory tests performed since last interview

Test	Date	Result (units)	Test	Date	Result (units)

MEDICINES TAKEN SINCE LAST INTERVIEW

ARV medicines	Dosage	Frequency	Start date	Stop date	Continues	Stop reasone	Adherencef
					☐		
					☐		
					☐		

Other medicines and traditional medicines	Dosage	Frequency	Route	Start date	Stop date	Continues	Stop reasone	Indication
						☐		
						☐		
						☐		

NEW MEDICINES PRESCRIBED AT THIS INTERVIEW

NEW ARV medicines	Dosage	Frequency	Start date	Quantity supplied	Batch number

Other NEW medicines	Dosage	Frequency	Route	Start date	Quantity supplied	Indication

STOP REASON[e]
1 Adverse event
2 Poor adherence
3 Course completed
4 Planned interruption
5 Planned medication change
6 No longer needed
7 Treatment failure
8 Pregnancy
9 Drug out of stock
10 Cost
11 Patient decision
12 Died
13 Lost to follow-up
14 Other (please specify)

ADHERENCE[f]
A Adequate
P Poor

CEM focal person ..... **Phone** ..... **Date of next appointment** dd / mm / yy

Guidelines for completion of TREATMENT REVIEW FORM

A TREATMENT REVIEW FORM should be completed each time an enrolled patient is reviewed after starting treatment with the monitored ART medicines. This form should also be used to follow up infants who have been exposed to ART *in utero* and/or who are receiving ART for PMTCT.

Patient CEM ID: The Patient CEM ID is the number used by the CEM programme to identify the patient. This number should be recorded on the treatment initiation form and on each subsequent treatment review form.

Mother's CEM ID (for INFANTS): If you are completing a TREATMENT REVIEW FORM for an infant who has been exposed to ART *in utero* and/or who is receiving ART for PMTCT, please ensure that both the **mother's** and the **infant's CEM ID** are recorded on the form.

Tick boxes (☐): Please mark boxes with a tick ☑ where appropriate.

TREATMENT PROVIDER

Patient file number: Record the number you use to identify the patient at your clinic.

MEDICAL DETAILS

Weight and height: Record the patient's current weight. Height should be recorded for children at treatment review, but is unnecessary for adults if already recorded at treatment initiation.

Indication for ART: Indicate whether ART is being used for **Treatment** of the patient's HIV infection or for **Prevention of mother to child transmission** (PMTCT), or for **Both** reasons.

Pregnant: Indicate whether the patient is pregnant, not pregnant, or uncertain. If pregnant, record the current gestation in months.

EVENTS

New events since last interview: Please record:

- all **new health events** that have occurred since the patient started the monitored medicine
- any **deterioration or improvement in pre-existing conditions** (or previously recorded events)
- **death** (including cause of death, if known)
- **pregnancy-related conditions** including: **complications** (e.g. gestational diabetes, pregnancy induced hypertension, preeclampsia, threatened miscarriage); **type of delivery** (e.g. normal delivery, caesarean section); **pregnancy outcome** (e.g. miscarriage, abortion, stillbirth, live infant, multiple birth).

For Infants exposed to ART *in utero* please include the following EVENTS, if applicable: **congenital malformation** (describe); **condition of infant at birth** (e.g. low birth weight); all **new health events** (e.g. illness of any type, failure to thrive); **death** (including cause of death, if known).

For each event, select the appropriate **code** for **outcome, severity, seriousness** and **rechallenge** from the shaded panel below the EVENTS section.

LABORATORY TESTS

Tests and results: Record the results (including *units*) of any laboratory tests performed in the PAST 30 DAYS.

MEDICINES TAKEN SINCE LAST INTERVIEW

Antiretroviral medicines: ART medicines may be recorded either as individual medicines or as fixed dose combinations (FDCs). Standard ART abbreviations may be used. Include start and stop dates for medicines that were started or stopped during the interval since the patient was last interviewed and indicate which medicines continue to be taken by ticking the box in the **continues** column ☑. For medicines that have been stopped, select the **reason(s) for stopping** from the list of **codes** provided (more than one code may be used). For ART medicines, please also select the appropriate **adherence code**.

If there has been no change to a previously prescribed medicine, just write the name of the medicine and tick the box to indicate that the medicine continues ☑.

Note: If a medicine was stopped and later restarted, please include separate entries for each course. If the dose was changed, record the medicine again on a new line with the new dose and dates of administration.

Other medicines: Record the details of other medicines, including over-the-counter medicines and any traditional medicines, herbal remedies or health supplements taken since the last interview.

NEW MEDICINES PRESCRIBED at this interview

ARV medicines and other medicines: Record the details of all **new medicines** prescribed at this interview. ART medicines may be recorded either as individual medicines or as FDCs. Standard ART abbreviations may be used.

Quantity supplied: Please indicate the number of days supply or the number of tablets provided (or the volume for a suspension), including the units (days, tablets or ml).

Annex 5. Patient ID card – suggested content

Front

Patient Card

Monitoring of HIV medicines

Country organization/logo

Name of clinic: .....

Name of patient: .....

Unique no: .....

Please bring this card during every visit to any hospital or clinic

Back

Cohort event monitoring (CEM) programme

This patient's medicines are being specially monitored to help decide the safest use and ensure the greatest benefits.

If he or she has any new health problems, please inform his or her regular clinic and identify the patient with the unique number

Clinic phone no: .....

Annex 6. Coding sheet for reviewing of events before data entry

TYPE OF EVENTS

Events in control period ☐ Events on treatment ☐

For events in the control period, event terms will be determined, but no other assessment will be undertaken.

REPORT ID

Patient initials: ..... Unique number: ..... Report number: .....

(*The report number is given by the PvC for events that occur on treatment.*)

MONITORED MEDICINES

Record the individual medicines or the ARV regimen

1. .....
2. .....
3. .....

ASSESSMENT OF INDIVIDUAL EVENTS

Event terms are selected by the clinical reviewer from the events dictionary

Dechallenge and rechallenge details

This assessment will be made on the monitored medicine(s) or regimen only

Events	Outcome[1]	Rechallenge[2]	Died[3]
1			
2			
3			
4			
5			
6			

Coding for the above as follows:

1. a, resolved; b, resolving; c, resolved with sequelae; d, not resolved; e, worse; f, died; g, unknown; h, medicine continued; i, dose reduced.
2. N, no rechallenge; +ve, recurrence; –ve, no recurrence; U, unknown outcome.
3. Died: DR, due to adverse reaction; DC, medicine may be contributory; UN, unrelated to medicine; DU, cause of death unknown.

Qualitative and relationship assessment

This assessment will be made on the monitored medicine or regimen only.

For events in the control period, there will be no assessment – just a list.

Events	Severity[a]	Seriousness[b]	Duration[c]	Relationship[d]
1				
2				
3				
4				
5				
6				

Coding for the above as follows:

a. Severity:1. not severe; 2. mild; 3. moderate; 4. severe.
b. Seriousness: D, died; L, life-threatening; H, hospitalization; Dis, permanent disability; C, congenital anomaly.
c. Duration to onset: date medicine begun to date of onset of event, calculated in days.
d. Relationship: 1,.definite; 2,.probable; 3,.possible; 4,.unlikely; 5,.unclassified; 6,.unclassifiable.

CLINICAL GROUPS FOR EACH EVENT

Enter the appropriate Clinical Group for each event: this can be abbreviated to the first 3 letters of each group.

Clinical Group	1	2	3	4	5	6

Date of completion: ...../...../..... Clinical reviewer: .....

Annex 7. Major clinical categories in CEM events dictionary

1. Accidents
2. Alimentary
3. Autonomic
4. Circulatory
5. Concomitant medicines (associated events)
6. Died
7. Device
8. Endocrine/metabolic
9. Ear, nose and throat
10. Eyes
11. Haematological
12. Hepatobiliary
13. Immunological
14. Infections
15. Lactation exposure
16. Musculoskeletal
17. Neoplasms
18. Neurological
19. Poisoning
20. Pregnancy register
21. Mental health disorders
22. Reproductive organs
23. Respiratory
24. Skin
25. Surgery
26. Unclassified
27. Urological

Annex 8. Example of events collation

Circulatory events with omeprazole (from the (The New Zealand) Intensive Medicines Monitoring Programme (IMMP))

OMEPRAZOLE

Event	Sex	Age	Dose	Dur	Rel	Report No.
Circulatory cont …						
CHF, worse	F	82	40	23 m	4	R 28103 (D)
CHF, worse	F	71	20		4	F 32450 (D)
CHF, worse	F	79	20	1 d	4	F 32486 (D)
CHF, worse	M	82	20	18 m	4	S 33597
CHF, worse	M	71	20		4	F1/1581 (D)
CHF, worse	M	70	20		4	P1/1909
CHF, worse	M		20	15 m	4	S1/2070 (D)
CHF, worse	F		40	2 y	4	S1/2076 (D)
CHF, worse	F		20	1 y	4	S1/2087
CHF, worse	F	77	20	8 m	4	F1/2395
LVF	M	85		16 m	4	S 30292 (D)
LVF	M	61	20	6 w	4	F 31254
LVF	M	68	20	2 y	4	S 33620 (D)
LVF	M	49	40		4	S 33679 (D)
LVF	M	83	20		4	F1/1584 (D)
LVF	M	78	20		4	F1/1906
LVF	M	76	20	14 m	4	F1/2689 (D)
Dyspnoea	F		20	10 m	4	F1/2109
Oedema	F		20		3	R 28310
Oedema	F		20	1 d	2	R 28484 *
Oedema	F	78	20	2 y	3	F 30247
Oedema	F	81	20	4 y	4	S 33689
Oedema	F		20		4	R1/1612
Oedema	M	79	20		4	P1/1787
Oedema	M	93	40	20 m	4	P1/2130
Oedema (nifedipine)	F	77	20		3	F 23855
Cardiomyopathy	F		40		4	S 33684 (D)

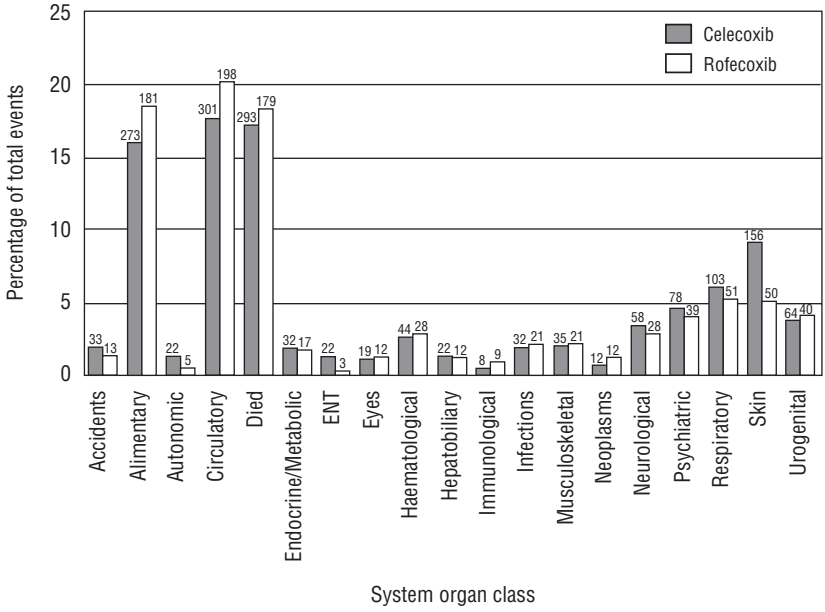
Event	Sex	Age	Dose	Dur	Rel	Report No.
Cardiac disease unspecified	M	73	40		4	F1/1067 (D)
Cardiac disease unspecified	F	73	40		4	F1/1100 (D)
Angina	F	82	40	14 m	4	F1/2302
Angina	M	78	40	18 m	4	F1/2468
Angina, unstable	M	71	20		4	P 30301
Angina, unstable	F	80	20	2 w	4	F 32463
Angina, unstable	M	46	40		4	F1/1856
Angina, unstable	F	74	20	3 m	4	S1/2059
Angina, unstable	M	68	40	3 y	4	S1/2501 *
Angina, unstable	F	66	40	9 m	4	F1/2528
Angina, worse	F	63	20	12 m	4	S 33616
Angina, worse	M	68	40		4	R1/1055
Angina, worse	M		20		4	F1/1614
Ischaemic heart disease	M	67	20		4	C1/1637 (D)
Ischaemic heart disease	M	74	20	21 m	4	S1/2525 (D)
Ischaemic heart disease, worse	F	82	20		4	F1/2295
Chest pain	F	52	20	14 m	4	S 33690
Chest pain	M	71	20	3 y	4	F 34332
Chest pain	F	72	20		4	F1/1578
Chest tightness (sumatriptan)	F	47	20	1 w	4	R 29316
Chest tightness (sumatriptan)	F	50	20	13 m	3	R 31924
Myocardial infarction	M	76	40	2 y	4	R 30296 (D)
Myocardial infarction	M		20	6 w	4	C 30321 (D)
Myocardial infarction	F	84	20		4	F 30406 (D)
Myocardial infarction	F	78	20	2 y	3	S 30995 (D)
Myocardial infarction	M	70	20	13 m	4	F 32439 (D)
Myocardial infarction	F	89	20	4 y	4	F 32441 (D)

Annex 9. Comparative events profiles

(The New Zealand) Intensive Medicines Monitoring Programme (IMMP) sample comparison (celecoxib and rofecoxib)

FIGURE 1

Profile of events for celecoxib (n=1714) and rofecoxib (n=982)



Annex 10. Pregnancy questionnaires A, B and C

LOGO

Antiretroviral therapy: Cohort event monitoring

A. Initial pregnancy questionnaire

Unique number: .....

(Unique number and HIV clinic number should be copied from previous questionnaires)

District: ..... Health unit: ..... Clinician/Team: .....

A. WOMAN'S DETAILS: **Patient HIV clinic number:** .....

First name: ..... Family name: .....

Date of birth: ...../...../..... **or** age (years): ..... (known or estimated)

Weight (kg): .....

Date most recent regimen of ART commenced: ...../...../.....

B. PREGNANCY DETAILS

LMP if known: ...../...../.....

Date when movements first felt by mother (estimated): ...../...../.....

Estimated weeks of pregnancy at current interview: ..... weeks

Has she attended an antenatal clinic for this pregnancy? ☐ Yes ☐ No

Name of antenatal clinic she has attended or will attend:

.....

Antenatal clinic number (if available): ..... Next antenatal appointment: ...../...../.....

At what stage of pregnancy was she first exposed to ART? ☐ 1st trimester ☐ 2nd trimester ☐ 3rd trimester

Number of past pregnancies ..... Number of live babies delivered .....

C. ANY ABNORMALITIES OF THIS PREGNANCY SO FAR?

Abnormalities of pregnancy: ☐ None

Description of pregnancy abnormalities	Date of onset (dd/mm/yyyy)
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....

The Pregnancy **Progress** Questionnaire will be used at further pregnancy follow-ups.
When baby has been born, please complete the Pregnancy **Outcome** Questionnaire.

Please return this questionnaire to the Pharmacovigilance Focal Person according to local procedure

Focal Person: Name: ..... Phone: .....

Date of completion: ...../...../..... Date of next appointment: ...../...../.....

LOGO

Antiretroviral therapy: Cohort event monitoring

B. Pregnancy progress questionnaire

Unique number: .....

(Unique number and HIV clinic number should be copied from previous questionnaires)

District: ..... Health unit: ..... Clinician/Team: .....

A. WOMAN'S DETAILS: **Patient HIV clinic number:** .....

First name: ..... Family name: .....

Date of birth: ...../...../..... **or** age (years): ..... (known or estimated)

Weight (kg): .....

B. ANTENATAL CLINIC

Name of antenatal clinic:

.....

Antenatal clinic number (if available): .....

C. STAGE OF PREGNANCY

Estimated **weeks of pregnancy** at current examination: ..... weeks

D. ANY ABNORMALITIES OF PREGNANCY?

Abnormalities of pregnancy: ☐ None

Description of pregnancy abnormalities	Date of onset (dd/mm/yyyy)
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....

Baby already born? ☐ Where?..... Date of birth: ...../...../.....

Miscarriage? ☐ Date: ...../...../.....

If baby has been born, please complete the Pregnancy **outcome** questionnaire

Date of next appointment at antenatal clinic: ...../...../.....

Please return this questionnaire to the Pharmacovigilance Focal Person according to local procedure

Focal Person: Name: ..... Phone: .....

Date of completion: ...../...../..... Date of next appointment: ...../...../.....

LOGO

Antiretroviral therapy: Cohort event monitoring
C. Pregnancy outcome questionnaire

Unique number: .....

(Unique number and HIV clinic number should be copied from previous questionnaires)

District: ..... Health unit: ..... Clinician/Team: .....

A. PLACE OF DELIVERY: .....
(If in a birthing unit or clinic, please give name and phone number)
Patient number at birthing unit (if available): .....
Contact person at place of birth: .....

B. WOMAN'S DETAILS: **Patient HIV clinic number:** .....

First name: ..... Family name: .....

Date of birth: ...../...../..... **or** age (years): ..... (known or estimated) Weight (kg): .....

C. ANTIRETROVIRAL THERAPY

Was the mother still on ART when baby was born? ☐ Yes ☐ No

ARV medicines

D. OUTCOME OF PREGNANCY

Date of birth: ...../...../.....

1. Abnormalities of pregnancy: ☐ None ☐ Don't know
Miscarriage? ☐ Date: ...../...../.....

Description of pregnancy abnormalities	Date of onset (dd/mm/yyyy)
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....

2. Abnormalities of labour (describe below) ☐ None ☐ Don't know

Description of abnormalities of labour

3. Abnormalities of foetus or infant ☐ Not examined ☐ Foetal death Date: ...../...../.....
☐ None identified at birth ☐ None identified at 3 months ☐ None identified at 1 year

Description of any abnormalities	Date identified
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....
	...../...../.....

Please return this questionnaire to the Pharmacovigilance Focal Person according to local procedure

Focal Person: Name: ..... Phone: .....

Date of completion: ...../...../..... Date of next appointment: ...../...../.....

Annex 11. Table of collation of deaths (as events)

(With omeprazole, from the (The New Zealand) Intensive Medicines Monitoring Programme (IMMP))

OMEPRAZOLE

DIED

Circulatory cont …

Event	Sex	Age	Dose mg/day	Dur	Rel	Report No.
Vascular disease	F	74	20	17m	4	SI/2814(D)
Vascular occlusion	M	62	40	1d	4	FI/2285(D)
Venous thrombosis, embolism pulmonary, bronchopneumonia	M	87	20	1y	4	F33114(D)
Ventricular fibrillation, CHF	M	74	20	3m	4	C33504(D)
Endocrine/Metabolic						
Addison's disease	M		20	2y	4	S36594(D)
Alcoholism	M	67	20	4m	4	FI/2776(D)
Alpha 1 antitrypsin deficiency	F	55	40		4	S38674(D)
Cachexia	M	75	20	3y	4	FI/2779(D)
Debility	F	78	20	2y	4	FI/2945(D)
Dehydration	M	75	20	3y	4	FI/2399(D)
Dehydration, renal failure	F	81	20	17m	4	SI/2443(D)
Diabetes mellitus	M	88	20	16m	4	S34537(D)
Haematological						
Aplastic anaemia	F	86	20	18m	3	S28676(D)
Aplastic anaemia (leukaemia)	F	24	40	3m	4	FI/2373(D)
Bleeding disorder, renal failure	F		20	2y	4	S27986(D)
Bleeding, bowel	F	86	20	16m	4	C32989(D)
Leukaemia	M	80	20	10m	4	F33027(D)
Leukaemia	M	28	20		5	CI/1165(D)
Leukaemia, acute myeloid	F	54		1w	4	FI/1227(D)
Macroglobulinaemia	M	68	20	1w	4	CI/2032(D)
Myelodysplasia	F	68	40	4m	4	F32540(D)
Myelodysplastic syndrome	F	93	20	2y	4	SI/2606(D)

Event	Sex	Age	Dose mg/day	Dur	Rel	Report No.
Myelodysplastic syndrome, pulmonary fibrosis	F	81	40		4	CI/1271(D)
Myeloproliferative disorder	M	83	20	2m	4	FI/2810(D)
Hepatobiliary						
Biliary cirrhosis	F	66	40	20m	4	FI/2812(D)
Hepatic cirrhosis	M	74	20	18m	4	S33223(D)
Hepatic cirrhosis	F	60	20		4	CI/2383(D)
Hepatic cirrhosis	M	60	40		4	CI/2408(D)
Hepatic failure	M	77	40	1m	4	FI/5654(D)
Hepatic failure	M	62	20	5m	4	FI/2863(D)
Hepatic failure (azathioprine)	M	31	20		4	RI/1587(D)
Liver disease alcoholic	M	66	40	2y	4	S33689(D)
Immunological						
HIV/AIDS	M	40	20	4m	4	FI/2305(D)
Myocarditis, MI	F	78	20	2y	3	S30915(D)

Dur, duration to onset of event: h, hours; d, days; w, weeks; m, months.

Rel, relationship: 1, certain; 2, probable; 3, possible; 4, unlikely; 5, unclassified; 6, unassessable.

Annex 12. Table of eye events with COX-2 inhibitors illustrating a signal

(from (The New Zealand) Intensive Medicines Monitoring Programme (IMMP))

Demonstration of a signal

Disturbance of retinal circulation causing visual field defect, temporary blindness, visual disturbance and loss of acuity.

Nonspecific								
Event	**Code**	**Sex**	**Age**	**Drug**	**Dose**	**Dur**	**Rel**	**Report No.**
Eye pain	10.000	M	59	CEL	200	6 d	1	R52816*
Eye pain	10.000	F	71	CEL	200	738 d	4	F53137
Eye pain	10.000	M		CEL	200	287 d	4	F60469*
Eye pain	10.000	F	52	CEL	100	835 d	4	F60564
Eyes irritable	10.020	M	70	CEL	400		4	F56205
Eyes irritable	10.020	F	67	CEL	100	785 d	4	F62704
Eyes irritable	10.020	M	71	ROF			4	F58175
Eyes irritable	10.020	F	64	ROF	12.5	447 d	4	F69660
Red eyes	10.100	M		CEL	200	287 d	4	F60069*
Red eyes	10.100	F	64	CEL	100	620 d	4	F62269
Dry eyes	10.300	M	54	ROF	25	143 d	4	F60155
Visual								
Acuity								
Blurred vision	20.100	F	53	CEL	200	4 m	2	R46379*
Blurred vision	20.100	F	59	CEL	200	7 w	2	A47419*
Blurred vision	20.100	F	79	CEL	200	4 m	3	F54575
Blurred vision	20.100	F	71	CEL	200	392 d	4	F56537
Blurred vision	20.100	F	41	VAD		1 d	3	R59759*
Blurred vision (atenolol)	20.100	M	58	ROF		10 d	3	R478404*
Blurred vision (cilazapril)	20.100	F	81	ETO	60	42 d	2	A56946*
Vision abnormal	20.100	F	71	CEL	200		2	F50058*
Vision abnormal	20.100	F	73	CEL	200		2	R52142*
Vision abnormal	20.100	M	45	CEL	200	76 d	3	F52120
Vision abnormal	20.100	M	86	ETO	120	21 d	2	F60305*
Vision reduced	20.200	F	81	CEL	200	27 d	2	646049*
Vision reduced	20.200	F	74	CEL	200		3	P55508

Event	Code	Sex	Age	Drug	Dose	Dur	Rel	Report No.
Vision reduced	20.200	F	78	ETO	60	1 d	2	R607460*
Vision reduced	20.200	M	78	ROF	50	1 d	2	R50797*
Vision reduced	20.200	F	88	ROF	25		2	F57153*
Visual field defect	20.220	M	81	CEL	100	3 w	1	R50269*
Visual field defect	20.220	M	61	ROF	25	26 d	2	F53280*
Blindness temporary	20.310	M	78	ROF	50	1d	2	F58471*
Disturbance								
Flashing	20.500	M	77	CEL	200	8 m	4	F53547
Flashing	20.500	F	78	CEL	200	188 d	4	F59624*
Teichopsia	20.550	F	72	ETO	60	184 d	3	F61676
Teichopsia	20.550	M	77	ROF	12.5		2	B47874*
Teichopsia	20.550	F	73	ROF	12.5	2 d	2	A56985*
Intraocular								
Retinal haemorrhage	30.100	M	84	ROF	25	15 w	4	F53051
Vitreous detachment	35.000	F	65	CEL	100	869 d	4	F59161
Vitreous detachment	35.000	F	65	ROF	12.5	8 m	4	F53246
Cataract	40.000	F	78	CEL	200	46 d	4	F59324*
Cataract, worse	40.000	F	84	CEL	200		4	F57441
Glaucoma	50.000	M	74	CEL	200		3	F59252*
Uveitis posterior	60.010	F	67	CEL	200		4	
Comeal								
Keratitis	70.200	M	46	CEL	299	640 d	4	F58745
Keratitis	70.200	F	70	ROF	12.5		4	F54854*
Conjunctival								
Infection								
Conjunctivitis	80.000	F	61	CEL	200		4	F54944
Conjunctivitis	80.000	F	77	CEL	200	49 d	4	F50177*
Conjunctivitis	80.000	F	53	CEL	200	8 d	4	F57163
Conjunctivitis	80.000	F	42	CEL	200	113 d	4	F52138
Conjunctivitis	80.000	F	56	CEL	400	27 m	4	F53139
Conjunctivitis	80.000	F	76	CEL	100	46 d	4	F59424

Event	Code	Sex	Age	Drug	Dose	Dur	Rel	Report No.
Conjunctivitis	80.000	F	53	CEL	100	890 d	4	P559550
Conjunctivitis	80.000	F	55	ROF	50		1	R56688*
Allergy								
Conjunctivitis allergic	80.050	M	43	CEL	200	1 w	3	B43081*
Conjunctivitis allergic	80.050	F	46	ROF	25	4 m	4	F59972
Haemorrhage								
Subconjunctival haemorrhage	80.200	M	68	CEL	400	531 d	4	F58012
Subconjunctival haemorrhage	80.200	F	83	CEL	100	12 d	4	F60120
Subconjunctival haemorrhage (azathioprine, prednisone)	80.200	F	68	ROF	25	307 d	3	F56344
Eyelid								
Blepharitis	80.300	F	59	CEL	700	5 m	4	F54489
Meibomian cyst	80.360	F	54	CEL	200	6 m	4	F57543

Key:

Code, event dictionary code.

Dose, mg/day.

Dur, duration to onset of event: mi, minutes. h, hours, d, days, w, weeks, m, months.

Rel, relationship: 1, certain, 2, probable, 3, possible, 4, unlikely, 5, unclassified, 6, unassessable.

Suffix to report number: *, medicine withdrawn; (D), patient died.

CEL: celecoxib; ROF: rofecoxib; VAD: valdecoxib; ETO: etdolac

Annex 13. Example of collation of concomitant drug events with celecoxib

(From (The New Zealand) Intensive Medicines Monitoring Programme (IMMP))

Events by concomitant medicine

Event	Sex	Age	Dose mg/d	Dur	Re	Report No.
Alendronate, gastric ulcer bleeding, anaemia	F	89	100	1 m	3	R 49222 *
Allopurinol, duodenal ulcer, oesophagitis	M	52	200		4	B 46665*
Allopurinol, renal failure acute	F	71	200		3	R 47848*
Amiodarone, dyspnoea	F	79	400	7 d	2	R 48563 *
Amitriptyline, hypertension, hemianopia	F	80			3	B 42818
Amitriptyline, myocardial infarction	F	80	200	5 d	3	R 43633 *
Amitriptyline, tachycardia	F	45	200	3 d	3	R 44655 *
Aspirin, duodenal ulcer bleeding	F	82	100	2 m	3	B 45376 *
Aspirin, gastric ulcer bleeding	F	70	200	5 m	3	F 50693 *
Aspirin, gastric ulcer bleeding, anaemia	F	89	100	1 m	2	R 48722 *
Aspirin, haematemesis, melena, duodenal ulcer	M	72	200	3 w	3	B 47881 *
Aspirin, melena, myocardial infarction	M	71			3	D 48943 *
Bendrofluazide, dyspnoea, weakness	F	84		19 m	2	R 51808 *
Bupropion, anxiety, insomnia	F	64	100	1 m	4	D 41552
Cilazapril, dyspnoea, weakness	F	84		19 m	2	R 51298 *
Cisapride, vomiting, hysteria, hypokinesia	F	47	100	1 d	4	R 46338
Diclofenac, nephritis interstitial	M	73		6 w	3	R 46646 *
Hair dye, urticaria, angioedema, wheeze	F	74	200	1 h	2	B 43835 *
Hepatitis B vaccine, flushing, dizziness, skin cold clammy, malaise	F	42	100	15 mi	4	R 50467
Ibuprofen, LFTs abnormal	F	61	200	1 m	3	B 47516
Leflunamide, liver injury cholestatic	F	65	200	8 m	4	R 48407 *
Leflunomide, tendon rupture, arm pain	M	48			4	R 47912

Event	Sex	Age	Dose mg/d	Dur	Re	Report No.
Methotrexate, liver injury cholestatic	F	65	200	14 m	4	R 47417 *
Metoprolol, angioedema	F	73	200		4	R 52124
Olanzapine, akathisia	F	69	200	16 d	4	R 50436 *
Pantoprazole, rash	F	78	100	3 d	4	R 46646
Paroxetine, hyponatraemia	F	79	200	2 d	4	R 45502 *
Perfume, anaphylactoid reaction	F	60	200		4	R 56462 *
Prednisone, chest pain	F	57	400	2 h	3	B 46877 *
Prednisone, duodenal ulcer	F	84	200	12 d	3	R 46489 *
Prednisone, haematemesis	M	55	200	4 m	3	B 44195 (D)
Prednisone, melena	F	94	400	5 d	3	R 47140 *
Prednisone, tendon rupture, arm pain	M	48			4	R 41312
Quinapril, cough, dyspnoea	M	72	200	1 w	4	R 47288 *
Quinapril, headache, dental caries, hypertension, therapeutic response decreased	M	67	200	3 m	2	B 43831 *
Quinapril, urticaria, angioedema, wheeze	F	74	200		3	B 43849 *
Quinine, thrombocyotpaenia, bleeding	F	53	200	7 d	3	B 44505 *
Spironolactone, hyponatraemia	F	86	100		3	F 51665 *
Sulphasalazine, bladder discomfort, rash papular, pruritus	F	68	200		4	R 47589 DR
Synvisc, pain joint	F	41	200	1 d	4	R 48246
Warfarin, INR increased	F	87	200	9 d	2	R 48931 ‘
Warfarin, INR increased	F	69	200	3 d	3	R 49106
Warfarin, INR increased, haematuria	M	59	400	1 d	2	B 41355 *
Warfarin, aortic aneurysm ruptured	M	78	200	6 w	4	R 48024 (D)

Key:

mg/d, mg/day; Dur, duration to onset of event: mi, minutes; h, hours; d, days; w, weeks; m, months.

Re, relationship; *, medicine withdrawn; DR, dose reduced; (D), patient died.

Annex 14. Advice on communication

The importance of communication

Throughout this manual effective communication has been mentioned as an essential part of good pharmacovigilance. This section gives an overview of some of the most important knowledge and skills in communication, without which even the best system will not fulfil its potential. The method and quality of professional communication is as important as the message itself.

Know your audience

It is critical to tailor all your materials and activities closely to the abilities and preferences of your many audiences. These days, even very serious people have little time or short attention spans for printed materials especially, and everything needs to be as brief, clear and persuasive as possible. Not everyone will share your priorities and values, understand them or care about them, so it's important to know the state of mind of your recipients so that you deliver your message in a way that really does get under their skin. Remember that within just one audience (pharmacists, for example) there will be a very wide range of ability, literacy, motivation and so on. Get to know your audiences through direct engagement and exchange with them: such knowledge will pay dividends. One message in one format will never be suitable for all your audiences.

Seek feedback

One of the best ways to understand your audiences is to actively seek feedback from them about your materials and what you are doing. Always pilot a project like the production of a reporting form or a new explanatory leaflet: find out what a range of recipients think about your work and then modify the content and the approach in the light of their views. Those of us working at desks in centralized offices often misjudge the minds of our recipients and so our messages don't get the attention they deserve or the response we hope for. Involve your audiences and constantly seek their views.

Give feedback and provide benefits

To stimulate collaboration and motivate colleagues, there needs to be some real benefit from making the effort to report adverse drug reactions (ADRs), or to monitor public health programmes, or take part in other activities. At the lowest level, appreciation (a "pat on the back") is an essential, powerful motivator, but feedback about how information has helped improve patient safety, or a special newsletter for reporters and collaborators, or any other

acceptable incentive will make a difference. There are still too many systems in which doctors, nurses and pharmacists are expected to help, but get no acknowledgement, appreciation or feedback at all. We cannot simply rely on people helping us without active encouragement.

Make your communications stand out

The competition for everyone's attention at every moment of the day is extreme, and health care professionals the world over are buried in printed materials of all kinds – many of them attractive, impressive and influential, but many of them are still put in the bin without so much as a glance.

We need to be sure that our materials look attractive and professional and, as far as possible, irresistible! Reporting forms need to look engaging and inviting, not merely amateurish attempts made on a word processor and printed in black and white. Some input from a graphic designer will make all the difference to the quality (and success) of forms and every piece of printed or electronic material. There may be a small initial cost, but that will be offset by the reduction in forms wasted and thrown away, and in increased interest and involvement. We are competing for people's attention, and need to take that challenge seriously. (Just look in any decent magazine and see how elegantly and powerfully commercial messages are promoted. Notice how important pictures and visual quality are in successful commmunications.)

Writing style

Writing is another of those advanced skills which every pharmacovigilance professional is expected to be born with. Good writing is hard work and essential for effective communication. Try to use people whose writing skills are advanced already, but if there is no-one like that, follow these rules:

- Write in the simplest, clearest language suitable for the task.
- Get your main points over at the beginning, and repeat them at the end.
- Keep sentences and paragraphs short.
- Use subheadings and bullet points as much as you can.
- When there is a lot of subsidiary or supporting material, try to separate it from the main message content, and put it at the end.
- Read your writing aloud to see how it sounds – this is one of the best tests possible.
- Get some members of your intended audience to read and comment on what you have written.
- Try to use pictures and simple graphics to support your words.

Repeat the message

Remember that in the hurly-burly of workaday life, many people will miss a message which is sent only once. *One communication is no communication*. Repeat your message again and again, in different forms and through different channels, until you know that people have received it and are being influenced by it – and that might take years rather than months. And then keep going: if people are not constantly reminded, they will forget. Changing people's attitudes, values and behaviour takes an immense amount of time and effort.

Get personal

The closer your communications get to being one-to-one, face-to-face, the more effective they will be. A mailing of a thousand leaflets will have far less effect than ten mailings of ten leaflets carefully tailored to subgroups of the audience. And, of course, mailings will have far less effect than meeting people in small groups or individually. Within the limits of your budget and resources, get as personally close to your recipients as you can.

Journalists

The media in all its forms can become powerful allies of health care and patient safety if journalists are dealt with personally and professionally. Most bad press comes from alienated journalists who have never been contacted, briefed, or educated on the complexities of medicine. Get some training in media relations; meet some of your local editors and health journalists; explore what you can achieve together. Suspicion and avoidance simply generate more suspicion and hostility. (The UMC publication *Dialogue in pharmacovigilance* contains guidance on media relations, and there are lots of books and useful websites.) And – never say, "No comment".

Meetings

Meetings are the form of group communication which probably cause more anxiety and frustration, and waste more time than any other single activity. While they are sometimes productive, they are often depressing and demoralizing. Meetings can be well-run, short, effective and uplifting. Running effective meetings requires a very specific set of knowledge and skills which can be learnt by anyone keen enough to reduce the percentage of their own and other people's lives wasted sitting pointlessly in meeting rooms. Again, there are lots of good books and web sites which will reveal how staff meetings, seminars, conferences and consultations can be made stimulating and productive. At the beginning of a meeting always ask these two questions:

(1) What are we hoping to achieve? and

(2) How long will this meeting last?

(Meetings without a time limit will simply expand to fill any amount of time available.)

The message

The safety of patients worldwide is served by dedicated professionals doing their work well, but that work will never reach its considerable potential without excellent supporting communications. Excellent communications require a degree of expertise, creativity and skill which not all officials and scientists have as a matter of course. In every organization there is likely to be someone with a communications gift: look for them and use them if you can; otherwise put communications on your regular agenda as a high priority and give the activity of communicating as much attention as the content of what you wish to communicate. Failure to pay attention to the complexity and demands of effective communication lies at the heart of many of the most serious failures throughout health care and regulation.

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Annex 15. Resources

1. USEFUL WEB SITES

WHO Headquarters

A great deal of information is available here, including access to WHO publications.

http://www.who.int/

EMP/QSM

www.who.int/medicines/areas/qualitysafety/safetyefficacy/pharmvigi/en/index.html

HIV Programme

www.who.int/hiv/topics/pharmacovigilance/en/index.html

www.who.int/entity/hiv/pub/toolkits/3-2-8_Pharmacovigilance

The Uppsala Monitoring Centre (UMC)

This site provides very useful information about practical pharmacovigilance including definitions and advice on pharmacovigilance policy.

http://www.who-umc.org/

www.who-umc.org/DynPage.aspx

Vigisearch

Provides access to the WHO worldwide database of adverse reactions and dictionaries: *Open DD-online* (Drug Dictionary), *Open ATC-online* (ATC classification) and *Open WHO-ART-online* (adverse reaction terminology).

https://vigisearch.who-umc.org/login.asp

European Medicines Agency

This is a useful resource on product information, current issues and regulatory actions.

http://www.emea.europa.eu

Food and Drug Administration (FDA), USA

This is a useful resource on product information, current issues and regulatory actions.

http://www.fda.gov/

Communicable Diseases Centre, USA

This site has a lot of information and statistics on communicable diseases and medicines related to their treatment.

http://www.cdc.gov/

New Zealand regulatory web site

This is a good resource for datasheets for medicines and patient leaflets. It also has articles in *Prescriber update*, many of which come from the National Pharmacovigilance Centre.

http://www.medsafe.govt.nz/

Natural Standard

The best and most authoritative web site available on herbal medicines. Users are required to register and pay a fee.

http://www.naturalstandard.com/

British National Formulary

A good and reliable resource for information on medicines.

http://bnf.org/bnf/

Literature resource

The WHO Health Inter-Network Access to Research Initiative (HINARI). This provides free or very low-cost online access to the major journals in biomedical and related social sciences to local, not-for-profit institutions in developing countries.

http://www.who.int/hinari/about/en

Micromedex/Drugdex/Martindale

All are available through this web site. Users are required to register and pay a fee. This is probably the most convenient and comprehensive source of information on medicines.

https://www.thomsonhc.com/home/dispatch/PFDefaultActionId/pf.LoginAction/ssl/true

PubMed

This is a good literature resource. Abstracts are available free.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed

Anatomical Therapeutic Chemical (ATC) Classification and codes

The ATC classification system is maintained by the WHO Collaborating Centre for Drug Statistics Methodology

http://www.whocc.no/atcddd/

International Society of Pharmacovigilance (ISOP)

This is an important international society. Their web site gives information about meetings and training courses.

www.isoponline.org

International Society for Pharmacoepidemiology (ISPE)

This site is a useful source of information on the activities of the society and for guidelines on risk management and links to relevant information.

www.pharmacoepi.org

International Uniform Requirements for Manuscripts Submitted to Biomedical Journals

An essential resource when writing articles, this site gives guidance on structure of articles and formats for references.

http://www.icmje.org/

British Medical Journal (BMJ)

Free access to some articles is available and the table of contents for each issue can be seen.

http://bmj.bmjjournals.com/

Medline

This site gives access to a list of journal abbreviations. It is an essential resource for compiling literature references and checking the details of journals referred to in articles in the literature.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Journals&itool=toolbar

Cytochrome P450 enzymes

A listing of the enzymes with the medicines affected is provided. This is a useful resource when researching possible interactions.

http://medicine.iupui.edu/flockhart/table.htm

International Classification of Diseases (ICD-10)

An electronic searchable version of ICD-10 is available on this web site.

http://www.who.int/classifications/apps/icd/icd10online/

2. PUBLISHED RESOURCES

Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala, Sweden, The Uppsala Monitoring Centre, 2000.

Safety of medicines: A guide to detecting and reporting adverse drug reactions. Geneva, World Health Organization, 2002.

The Importance of pharmacovigilance: Safety Monitoring of medicinal products. Geneva, World Health Organization, 2002.

The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool. Geneva, World Health Organization, 2006.

Hugman B. Healthcare communication. London, Pharmaceutical Press, 2009 (www.pharmpress.com).

Coulter DM. The New Zealand Intensive Medicines Monitoring Programme in pro-active safety surveillance. *Pharmacoepidemiology and Drug Safety*, 2000, 9:273–280.

Harrison-Woolrych M, Coulter DM. PEM in New Zealand. In: Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007:317–332.

Shakir Saad AW. PEM in the UK. In: Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007.

Coulter DM. Signal generation in the New Zealand Intensive Medicines Monitoring Programme. *Drug Safety*, 2002, 25:433–439.

Coulter DM. Privacy issues and the monitoring of sumatriptan in the NZ IMMP. *Pharmacoepidemiology and Drug Safety*, 2001, 10:663–667.

Reporting adverse drug reactions: Definitions of terms and criteria for their use. Geneva, Council for International Organizations of Medical Sciences (CIOMS), 1999.

Annex 16. Suggested standard operating procedures for CEM

The drafting of the standard operating procedures (SOPs) needs to take into account the following:

1. **What** needs to be done?
2. **Who** will do it?
3. **Where** will it be done?
4. **When** will it be done?
5. **How** will it be done?

The following list will not be complete. There are other tasks and functions in the local situation that will need SOPs if they are to be performed satisfactorily.

- Distributing and returning completed spontaneous reporting forms.
- Distributing the CEM questionnaires (for standard follow-up and pregnancy) to the sentinel sites, management of the questionnaires at the sites (including secure storage of completed questionnaires) and the return of the questionnaires to the CEM unit.
- The standard recording of ART (including doses) on the spontaneous reporting forms and CEM questionnaires. The aim is to make recording easy, but also very clear.
- The numbering, completion and checking of the questionnaires at the HIV clinics.
- The follow-up of non-attenders at the HIV clinic and the recording of any events.
- The follow-up of pregnant patients and the recording of all details on the questionnaires at the HIV clinic, antenatal clinic and birthing unit. Notification of when a baby is born to a mother on ART.
- The longer term follow-up of babies at 3 months and 1 year.
- Receiving the questionnaires at the CEM unit, giving each one a report number and the data entry.
- Checking with the health facilities when follow-up questionnaires for particular patients do not come through at the expected times.
- Collating and reviewing the events.

- Reviewing and acting on data for the special categories: serious events, pregnancies, lactation exposure, deaths, lack of efficacy.
- Good communication and coordination between CEM staff and PvC staff (if they are different) at the central office and incorporating the CEM events into the national database.
- Clinical review of the events.
- Reporting the results to the regulatory authority, advisory committee, health workers involved in the programme and health professionals generally.

Glossary

The definitions given below apply to the terms used in this Handbook. They may have different meanings in other contexts.

Active (or proactive) safety surveillance
Systems whereby active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records.

Adherence
Faithful adherence by the patient to the instructions for taking the medicine supplied.

Adverse event
Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse (drug) reaction (ADR)
A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Causality assessment
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event. Causality assessment is usually made according to established algorithms.

CemFlow
A sophisticated data management tool created by the UMC data entry and analysis in cohort event monitoring programmes.

Clinical trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.

Cohort event monitoring
A prospective observational cohort study of adverse events associated with one or more medicines.

Data-mining
At the UMC, this refers to the use of an automated tool, based on Bayesian logic, for the scanning of the WHO database (*Vigibase*) in the process of detecting adverse reactions associated with medicines: the Bayesian Confidence Propagating Neural Network (BCPNN). Knowledge-detection is the preferred term for the process.

Dechallenge
The withdrawal of a drug from a patient; the point from which the continuity, reduction or disappearance of adverse effects may be observed. The response to withdrawal may be followed over a period of time.

Effectiveness/risk
The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice.

Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from premarketing information, which is limited and based on selected subjects.

Efficacy
The ability of a drug to produce the intended effect as determined by scientific methods, for example in preclinical research conditions (opposite of hazard).

Individual case safety report (ICSR)
A report that contains information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient.

Lack of efficacy
Unexpected failure of a medicine to produce the intended effect as demonstrated by previous scientific investigation.

Medical Dictionary for Regulatory Activities (MedDRA)
The Medical Dictionary for Regulatory Activities is a medical terminology developed by the International Conference of Harmonisation with an emphasis on ease of use for data entry, retrieval, analysis, and display.

National pharmacovigilance centres
Organizations recognized by governments to represent their country in the WHO Programme (usually the drug regulatory agency). A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Rechallenge
The point at which a medicine suspected of causing an adverse reaction is re-administered either voluntarily or inadvertently to a patient.

Record linkage
Method of assembling information contained in two or more records, e.g. in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Regulatory authority
The legal authority in any country with the responsibility of regulating all matters relating to drugs.

Relationship assessment
The objective evaluation of the relationship between the administration of a medicine and a health event, taking into consideration duration of therapy to onset of event, response to dechallenge and rechallenge (if performed) and the presence of diseases or other medicines that could have caused the event. This process stops short of attempting to establish a causal relationship but is an essential preliminary.

Risk
The probability of harm being caused; the probability (chance, odds) of an occurrence.

Absolute risk
Risk in a population of exposed persons; the probability of an event affecting members of a particular population (e.g. 1 in 1 000). Absolute risk can be measured over time (*incidence*) or at a given time (*prevalence*).

Attributable risk
The risk associated with exposure to the monitored medicine(s). This is calculated by subtracting the background risk without the medicine(s) (reference risk) from the risk measured while taking the medicine(s).

Relative risk
Ratio of the risk in an exposed population (*absolute risk*) and the risk in an unexposed population (*reference risk*). Relative risk is the result of a relative comparison between outcome frequency measurements, e.g. incidences.

Reference risk
Risk in a population of unexposed persons; also called baseline risk. Reference risk can be measured over time (*incidence*) or at a given time (*prevalence*). The unexposed population refers to a reference population, as closely comparable to the exposed population as possible, apart from the exposure.

Serious adverse event or reaction
A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- is life-threatening;
- is a congenital anomaly/birth defect.

To ensure that there is no confusion or misunderstanding about the difference between the terms "serious" and "severe", the following note of clarification is provided:

> The term "severe" is not synonymous with serious. In the English language, "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on the outcome of the event on the patient or action criteria serves as the guide for defining regulatory reporting obligations.

Signal
Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

Spontaneous reporting
Unsolicited communication by health care professionals or consumers that describes one or more suspected adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Traditional medicine practice
The practice of traditional medicine involves the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Unexpected adverse reaction
An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from the characteristics of the drug.

VigiBase
The name for the WHO International ADR Database.

VigiFlow
VigiFlow is a sophisticated case-report management system created by the UMC for the submission of spontaneous adverse drug reaction reports.

WHO-ART
The WHO terminology for coding clinical information in relation to medicinal product therapy.