Pharmacovigilance Toolkit

This Pharmacovigilance (PV) Toolkit is a collection of resources and information needed for the practice of pharmacovigilance. The main aim of its development is to ensure that PV practitioners in low- and middle-income countries get access to information on the processes and activities involved in PV from a trusted source. The Toolkit contents are endorsed by the WHO Advisory Committee on the Safety of Medicinal Products after the original text has been written and reviewed by global experts.

In addition to this website, the Toolkit is available on USB drives in a similar format to this website, for use in areas with poor internet connectivity. The Toolkit is currently available in English, and efforts are underway to have it translated into other languages, although this is dependent on availability of volunteers and/or funding. The Toolkit will be reviewed periodically to ensure that it is abreast with developments in PV.

The Toolkit Management Team is keen to have your feedback such as what you think can be added, removed or modified in order to make its use more beneficial.

Disease-specific Toolkits

Although this PV Toolkit covers all the basics required for PV work, there are peculiarities when carrying out PV for certain diseases and subgroups of people. This has led to the development of the Malaria and HIV PV Toolkits, with a TB Toolkit currently being developed in addition. These disease-specific toolkits should be used in combination with the main PV Toolkit.
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About the Pharmacovigilance Toolkit
This Pharmacovigilance (PV) Toolkit is a package of simple PV tools and a description of supporting processes for the conduct of pharmacovigilance. The toolkit is developed and maintained by the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Ghana Medical School on behalf of the WHO Programme for International Drug Monitoring and in collaboration with WHO-HQ, Uppsala Monitoring Centre in Sweden and the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP). The governance framework for the toolkit and the process for adoption of content can be viewed below.

1. **Decision on content of toolkit** [Coordinated by Toolkit Maintenance Team – Abdul Malik Sulley, Alex Dodoo, Anna Hegerius & Cecilia Biriell]

2. **Development of content and writing of sections by experts**
   (e.g. Bruce Hugman for Communications; Ralph Edwards for Causality Assessment)

3. **Editing and proofreading by Toolkit Maintenance Team**

4. **Submission to UMC Editorial Team** (Alex Dodoo, Ralph Edwards, Marie Lindquist, Sten Olsson) and **WHO** (Shanthi Pal)

5. **Submission by WHO to ACSoMP**

6. **Upload of final approved file by WHO-CC, Accra**
What's new?

The World Medicines Situation 2011: Pharmacovigilance and Safety of Medicines

(http://apps.who.int/medicinedocs/documents/s18771en/s18771en.pdf)
1 Introduction

The safety of patients and the safe use of medicines are high priorities in the modern world. They are critical for the best health policy development and delivery of the best healthcare. They affect not only the welfare of patients but also the effective prevention and control of all kinds of diseases and the reduction of suffering and costs associated with them.

This Pharmacovigilance (PV) Toolkit is a package of simple PV tools and a description of supporting processes for the conduct of pharmacovigilance. It is targeted primarily at PV professionals in low and middle income countries, but is relevant everywhere PV is practised. It provides the framework and support needed for the effective conduct of pharmacovigilance at local, regional, national and international levels.

One of the essential aims of WHO and its partners is to provide countries with the necessary support and tools to be able to carry out pharmacovigilance activities effectively and in a harmonised way to ensure that data collected in each setting can be used globally. This current toolkit is one example of this work. It aims to provide countries with a complete guide, tools and assistance to undertake comprehensive pharmacovigilance according to WHO guidelines and recommendations and in line with contemporary best practice. It also provides a means of monitoring and evaluating activities using a novel pharmacovigilance indicator that all countries can use to measure performance. This is a much neglected area and deserves more attention if PV is to become more effective and continue to be funded.

Tell us what you think

The Toolkit Development and Management Teams are very keen to hear from you, what you think about the Toolkit and about ways in which you think it can be improved, what is missing, what is confusing or unclear. Please contact comments@pvtoolkit.org with your frank opinions.
1.1 What is pharmacovigilance?

Pharmacovigilance (PV) has been defined by the World Health Organization (WHO) as:

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem \(^1\,^2\).

It is an essential component of patient care and rational use of medicines. It is also variously referred to as

- adverse drug reaction monitoring
- drug safety surveillance
- side effect monitoring
- spontaneous reporting
- post-marketing surveillance

or variations of these.

Pharmacovigilance involves the safety monitoring of all medicines including herbal and complimentary remedies, vaccines and biological substances.

Harm related to use of medicines

The importance of pharmacovigilance in all countries is widely accepted in view of the well documented high rates of morbidity and mortality associated with use of medicines.

Many adverse drug reactions (ADRs) are preventable and a good knowledge of pharmacology, good prescribing practices and the provision of simple tools and facilities would reduce drug-related morbidity and mortality in humans. However, there are some ADRs which are unknown, unpredictable and not preventable though an understanding of the characteristics of patients likely to suffer such ADRs may help in

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\(^2\) Although the preferred term is medicine, the terms drug and medicine are used interchangeably in this document.
reducing their occurrence. It is also important to note that there will almost always be some drug-related problems which are unknown at the time the drug is registered for use.

This is because the information obtained during clinical trials of new drugs is by design insufficient to provide a comprehensive overview of its safety and also effectiveness in routine clinical practice. Examples of such limitations of pre-licensure clinical studies include short duration, small numbers of patients, exclusion of patients with other diseases, exclusion of pregnant women, infants and the elderly. The long-term safety of a medicine is thus only known when the drug is being used widely in a population and its safety is being monitoring by organized local, national and international efforts. Further information is available in the WHO (2002) publication "The importance of pharmacovigilance. Safety monitoring of medicinal products".

Initially, pharmacovigilance systems and activities were focused on adverse effects related to the intrinsic characteristics of drug substances, hence ‘adverse drug reactions’. In recent years, it has become apparent that a reduction of the global burden of morbidity and mortality related to medicines requires a broader, holistic look at all the factors leading to patient harm. The broadened patient safety scope of pharmacovigilance includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors. Counterfeiting, antimicrobial resistance, and the need for real time surveillance in mass vaccinations are other pharmacovigilance challenges which need to be addressed.

The ultimate safety decisions on medicines may need considerations of comparative benefit/risk evaluations between products for similar indications, so the complexity is great.

Pharmacovigilance in internationally funded programmes

In recent years, the international community has coordinated efforts to overcome the financial barriers to access to medicines by people living in poor countries. The establishment of the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM or
Global Fund) in 2002 has provided huge financial resources that have supplied hundreds of millions of doses of medicines for these three priority diseases. For instance, by the end of 2009 as a result of Global Fund funding:

- 2.5 million patients were able to start on antiretrovirals,
- 6 million treatments for tuberculosis (TB) have been provided
- hundreds of millions of doses of artemisinin-combination therapies have been deployed
- 104 million insecticide-treated nets have been distributed.

Mindful of the negative impact of drug-associated adverse events on patient care as well as adherence to treatment, the Global Fund Board in October 2002 recommended to Recipients that they

...implement mechanisms to encourage adherence to treatment (including but not limited to Fixed Dose Combinations (FDCs), once-a-day formulations, blister packs, and peer education and support), to monitor and contain resistance, and to monitor adverse drug reactions (ADRs) according to existing international guidelines and, if necessary, drawing on budgeted requests for financial support from the Fund.

Pharmacovigilance proposals for funding

A detailed analysis of the Global Fund Applications portfolio for Rounds 4-9 (2005-2010) however showed that of 431 individual Global Fund Proposals (166 for HIV, 120 for malaria and 145 for TB) examined, only 134 (31%) contained acceptable proposals for PV. These 431 applications were from 117 countries, 47 of whom are members of the WHO Programme for International Drug Monitoring. Eighteen countries indicated an awareness of PV in their applications but stated that the country had no PV systems nor undertook any PV activities whilst 21 countries made no mention at all of PV in their applications and procurement and supply chain management plans (PSMs). The

need to ensure that countries carry out systematic and continuous PV of all medicines is very clear.

The Global Fund and the World Health Organization together with other partners have developed a Global Pharmacovigilance Strategy. Though targeted at low-to-middle income countries, the strategy should resonate well with all countries including industrialised countries of the International Conference for the Harmonisation of Technical Requirements for the Registration of Pharmaceutical Products for Human Use (ICH countries). This Toolkit is an element in the larger global PV strategy. In addition, the WHO has developed a Technical Guidance note for Global Fund HIV Proposals to ensure that pharmacovigilance is included in these proposals.

(http://www.who.int/medicines/areas/quality_safety/safety_efficacy/TechnicalGuidancePharmacovigilance.pdf)

OR

2 Functions of a national pharmacovigilance system

The functions of a national pharmacovigilance system are numerous and varied. Through consultation between WHO, the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) and The Global Fund, the minimum functions of a national pharmacovigilance system have been defined to include the following:

1. To promote PV in the country, collect and manage ADR reports as well as reports of medication errors and suspected counterfeit/substandard drugs
2. To collaborate and harmonize with other ADR collection activities within the country (e.g. national disease control programmes, poison control centres, etc.) as well as international monitoring of ADRs in cohorts of defined patients
3. To identify signals of drug safety, i.e. unknown or poorly characterized adverse events in relation to a drug or drug combination and/or its use
4. To undertake assessment of risk and options for risk management
5. To identify if there are quality problems in medicines resulting in ADRs; and more generally, support the identification of medicine quality issues
6. To provide effective communication on aspects related to drug safety, including dispelling unfounded rumours of toxicity attributed to medicines and/or vaccines
7. To apply information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines
8. To develop and maintain drug utilization information
9. To identify issues associated with unregulated prescribing and dispensing of medicines.
2.1 Minimum requirements for a functional national pharmacovigilance system

Pharmacovigilance activities may be undertaken by several organizations, individuals and agencies. In most countries, the national system is organized and coordinated by the Ministry of Health or one of its agencies, typically the National Medicines Regulatory Authority. In some countries, it is undertaken by academic institutions, by hospitals or by independent legally-recognized organizations. No matter where pharmacovigilance is undertaken, the WHO in consultation with its Advisory Committee on the Safety of Medicinal Products (ACSoMP) and The Global Fund have agreed on core minimum requirements that should be present in any functional national pharmacovigilance system as follows:

1. A national pharmacovigilance centre with designated staff (at least one full time), stable basic funding, clear mandates, well defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring

2. The existence of a national spontaneous reporting system with a national individual case safety report (ICSR) form i.e. an adverse drug reaction (ADR) reporting form

3. A national database or system for collating and managing ADR reports

4. A national ADR or pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication

5. A clear strategy for routine and crisis communications
3 How to set up a pharmacovigilance centre

The setting up of a national PV centre requires several considerations. The WHO and UMC have produced a manual titled: “Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre” which contains Basic steps in setting up a Pharmacovigilance Centre, i.e.

1. Make contacts with the health authorities and with local, regional or national institutions and groups, working in clinical medicine, pharmacology and toxicology outlining the importance of the project and its purposes.
2. Design a reporting form and start collecting data by distributing it to hospital departments, family practitioners, etc.
3. Produce printed material to inform health professionals about definitions, aims and methods of the pharmacovigilance system.
4. Create the centre: staff, accommodation, phone, word processor, database management capability, bibliography etc.
5. Educate pharmacovigilance staff with regard, for example, to:
   - data collection and verification
   - interpreting and coding of adverse reaction descriptions
   - coding of drugs
   - case causality assessment
   - signal detection
   - risk management.
6. Establish a database (administrative system for the storage and retrieval of data).
7. Organize meetings in hospitals, academia and professional associations, explaining the principles and demands of pharmacovigilance and the importance of reporting.
8. Promote the importance of reporting adverse drug reactions through medical journals, other professional publications, and communications activities.

Further information on planning out these activities is provided in the manual, which is available free of charge from http://apps.who.int/medicinedocs/en/d/Jh2934e/.

The following chapters are included in the document:
1. Introduction
2. Why pharmacovigilance?
3. Definitions and aims
4. How to start a pharmacovigilance centre
5. Reporting of adverse drug reactions
6. Special issues in reporting
7. Practicalities in the organization of a pharmacovigilance centre
8. Assessment of case reports
9. Use of the data
10. Relations with other parties
11. Other sources of information
12. Funding
13. Glossary
14. Causality categories
15. WHO contacts

Further technical and advisory support is available from both the WHO (www.who.int/medcines/en) and the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (www.who-umc.org) web sites.

Support is also available from these organizations by contacting them by e-mail: empinfo@who.int or info@who-umc.org, or from the WHO Collaborating Centre for Training and Advocacy in Pharmacovigilance in Ghana: info@pvtoolkit.org
4 The WHO programme for International Drug Monitoring and how to join

4.1 The start of the programme

The first practical international co-operation in drug monitoring started in 1968. The ideas came up as a consequence of the so-called thalidomide tragedy. In the 1960s it was discovered that this medicine, thalidomide, could cause limb deformities in babies if ingested by mothers during pregnancy. This incident became the modern starting point of a science focusing on patient problems caused by the use of medicines. This science, and activities associated with it, is now most commonly called pharmacovigilance.

The Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) that reaffirmed the need for early action in regard to the rapid dissemination of information on adverse drug reactions and led, later to the creation of the WHO Pilot Research Project with 10 countries, to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. The initial activities of the pilot project culminated in the current WHO Programme for International Drug Monitoring and has grown to become a global network of national pharmacovigilance centres in over 140 countries (as at September 2011) around the world (see www.who-umc.org).

The intention of the WHO Programme is to ensure that early signs of previously unknown medicine-related safety problems are identified and information about them shared and acted upon throughout the world.

4.2 National centres in the programme

In each participating country the Ministry of Health, or equivalent, designates a National Centre for pharmacovigilance responsible for maintaining contacts with WHO on issues related to medicine safety. The network of national centres is coordinated by WHO and its Collaborating Centres (the WHO Collaborating Centre for International...
Drug Monitoring in Uppsala in Sweden, and lately, the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana and the WHO Collaborating Centre for Pharmacovigilance in Rabat, Morocco. The centre in Uppsala is usually called Uppsala Monitoring Centre or UMC. UMC is a foundation created by the Swedish government on the basis of an agreement between Sweden and WHO. According to this agreement WHO headquarters is responsible for all policy issues relating to the WHO Programme whilst UMC focuses on technical issues and the day to day running of the WHO Programme.

UMC manages a database of Individual Case Safety Reports (ICSRs) received from the national centres in the WHO network. The database, called VigiBase, currently (December 2011) contains almost 7 million descriptions of individual cases in which medicines, including vaccines, herbals and biologicals, have been suspected of contributing to an adverse reaction in a patient.

4.3 Benefits and obligations of being a member

When a country becomes a member of the Programme, it is essential that national centre personnel are fully aware of the benefits and obligations of membership.

Further information on the benefits of belonging to the WHO Programme can be obtained from WHO-UMC – Public Services – Pharmacovigilance - The WHO Programme - Joining the WHO Programme.

The main benefits include:

- Access to VigiBase (containing worldwide medicine safety data)
- Early information about potential safety hazards (based on analyses of worldwide data and communications from member countries)
- Terminologies and software (tools for carrying out national medicine safety tasks)
• Support, guidelines and resources (on pharmacovigilance practice) and access to the international network (knowledge and expertise of member countries).

In addition, members of the WHO Programme meet each year in a member country for the annual National Pharmacovigilance Centres meeting to share information and network.

4.4 Requirements for joining the WHO Programme for International Drug Monitoring

The basic requirements to join are:

1. General acquaintance with the methodology of spontaneous reporting

A country joining the WHO Programme must have a programme for collection of individual case safety reports (ICSRs) in place. The national programme should have reasonable funding to ensure continuity of operations and access to appropriate staffing and technical facilities. By operating the programme the managerial staff will acquire the necessary competence needed to interpret information coming from spontaneous adverse reaction reporting systems.

2. A national centre for pharmacovigilance

Only WHO member states can join the WHO Programme for International Drug Monitoring. Each state is represented by a National Centre authorized by the competent national health authority. The administrative affiliation of the National Centre varies between countries. In most cases the National Centre is part of the national drug regulatory authority but it may also be affiliated to a university institution, a hospital department or be integrated with a drug information or poison information service. A central technical advisory committee with expertise to evaluate reports and advise on suitable action is desirable.

3. Technical competence to fulfil reporting requirements to WHO

The main asset of the WHO Programme for International Drug Monitoring is its database of adverse reaction case reports submitted by the participating countries.
Case reports collected in the national drug monitoring programme must be submitted to the WHO Programme in a defined format. Before being admitted to the international scheme the National Centre has to demonstrate that it is capable of submitting data in the required format, as defined in the guidelines issued by UMC.

A new country is accepted in the Programme provided that individual case safety reports submitted to the WHO database (VigiBase) from that country may be freely available for analysis by any investigator, according to policy determined by the WHO. (Patient and reporter identity is not recorded in the WHO database).

4.5 How to join the WHO Programme for International Drug Monitoring

1. A formal application to be admitted as a member of the WHO Drug Monitoring Programme should be sent to WHO Headquarters, Geneva, by the competent health authority of the country. The application should identify the institution and responsible person representing the country as a National Centre in the WHO Programme. A country will be regarded as an Associate Member Country from the time the formal membership application is received. Associate Member Countries enjoy most of the services provided to full member countries.

2. A sample of at least 20 ICSRs collected in the national pharmacovigilance programme should be submitted to UMC. Reporting instructions may be obtained from UMC. Please note: This step may be taken simultaneously or even before a formal application is sent to WHO Headquarters. The sample reports will be subjected to a check for technical compatibility with the reporting requirements by UMC staff. Any deviation will be reported back to the National Centre. When compatibility of the reports is ensured, WHO Headquarters will be notified by UMC. The applying country will subsequently receive a confirmation from WHO Headquarters of its admittance to the Programme.

The steps involved in joining the WHO Programme are outlined in the flowchart below.
4.6 WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP)

The WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) was established in 2003 to provide advice to WHO, including its Collaborating Centres for the International Drug Monitoring Programme, and through it to the Member States of WHO, on safety issues relating to medicinal products. It provides advice to the WHO secretariat on general and specific issues related to Pharmacovigilance. It is composed of 12 members drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management and where appropriate, from other WHO expert advisory panels. Full details of the Committee can be obtained from:

Recommendations from the Committee's meetings can be obtained from:
5 Pharmacovigilance methods

Several methods can be used to collect safety information in pharmacovigilance. In all national pharmacovigilance systems, SPONTANEOUS REPORTING forms the bedrock of the system despite its well-known limitation of under-reporting. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other systems including active patient follow-up e.g. Cohort Event Monitoring (CEM). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2E Guidelines. The full document can be downloaded from the ICH website using this link http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html.

5.1 Passive surveillance

5.1.1 Spontaneous reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a national pharmacovigilance centre, pharmaceutical company, regulatory authority or other organization (e.g., WHO, Regional Centres, Poison Control Centre) 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.

Spontaneous reports play a major role in the identification of signals of drug related problems once a drug is marketed. They can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanyng spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since product launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.
5.1.2 Case series of spontaneous reports

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated frequently with drug therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore, when events such as these are spontaneously reported, it is important that pharmacovigilance centres place emphasis on these reports for detailed and rapid follow-up.

5.1.3 Targeted spontaneous reporting

This is a variant of spontaneous reporting. It focuses on capturing adverse drug reactions in a well defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns. The method is intended to ensure that patients are monitored and that adverse drug reactions are reported as a normal component of routine patient monitoring and standard of care. This focused approach has the same objectives and flow of information as for spontaneous reporting. The reporting requires no active measures to look for the particular syndromes.

5.2 Stimulated reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings), for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.
5.3 Active surveillance

Active surveillance, in contrast to spontaneous reporting, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug as in Cohort Event Monitoring. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a spontaneous reporting system.

5.3.1 Sentinel sites

Active surveillance can also be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups that would not be available in a spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

5.3.2 Drug event monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.
5.3.2.1 Cohort event monitoring

A modification of drug event monitoring is cohort event monitoring (CEM), an active pharmacovigilance method promoted by the World Health Organization and other agencies. In CEM, patients on a particular drug or groups of drugs are recruited at time of initiation of e.g. antiretroviral therapy (ART) and followed up by way of clinic or home visits or where appropriate by phone calls. A pre-treatment questionnaire is filled at time of recruitment and post-treatment questionnaires are filled at times of follow up which may either be once e.g. for anti-malarials or life-long e.g. for antiretrovirals. CEM also includes the possibility of following exposed pregnant women to ascertain any effect on the baby.

A complete Standard Operating Procedure for CEM is given in the appendices to this toolkit.

WHO has published Practical Handbooks on the Pharmacovigilance of Antimalarial Medicines and of Antiretroviral Medicines. See Literature resources in Chapter 11.1.

5.3.3 Registries

A patient registry is a list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry) or a specific exposure (drug registry). In each type of registry, which only differs by the type of patient data of interest, can be collected a battery of information using standardised questionnaires in a prospective fashion.

5.4 Comparative observational studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. A number of observational study designs are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

5.4.1 Cross-sectional study

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types
of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

5.4.2 Case-control study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups.

5.4.3 Cohort study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest or to study very rare outcomes.
5.5 Targeted clinical investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

5.6 Descriptive studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

5.6.1 Natural history of disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.
5.6.2 Drug utilization study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.
6 Definitions and terminologies in pharmacovigilance

The following definitions are used in the WHO Programme for International Drug Monitoring and member countries are encouraged to utilize them. Most of these definitions have been incorporated into guidelines issued by the ICH, EMEA and other competent national authorities. Full details, comments and explanatory notes for these are available in the Glossary of Terms from Uppsala Monitoring Centre (WHO-UMC – Public Services – Pharmacovigilance – Definitions – Glossary of Terms in Pharmacovigilance).

In spite of the above it is important to understand that there is a rapid change in the scope of pharmacovigilance and its practice. The move towards a greater patient safety focus, changes in legislation largely in the USA and the EU, and changes in databases and technology has caused some re-thinking of definitions. Some of this thinking is incorporated in the article Adverse drug reactions: definitions, diagnosis, and management⁴. Even this will be updated soon.

Of course, definitions are important so that we can converse and write about pharmacovigilance with greater clarity each of us knowing what the jargon means. Change upsets this so that below in italics newer definitions are accompanied by the reasons for changes.

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems⁵.


⁵ The Importance of Pharmacovigilance, Geneva, World Health Organisation, 2002
**Adverse reaction**

"A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

A more recent definition is:

**Adverse effect**

“An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

This definition can include medication error which is a major cause of adverse effects due to drugs, it includes harm from counterfeit drugs, it includes accidental overdose, it includes all medicinal products (so it includes delivery systems such as inhalers), it includes quality problems and excipients. This definition therefore includes adverse effects from a much broader range of causes. On the other hand the latter part of the definition focuses on the value of knowing about adverse effects: we want to know about those we can do something about in terms of prevention, diagnosis or treatment.

‘Adverse reaction’ and ‘adverse effect’ are interchangeable but adverse effect is more patient-centred, and adverse reaction is more drug-centred.

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6 WHO Technical Report No 498 (1972)

Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

Adverse event / Adverse experience

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.

Side effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

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.

This is considerably outmoded as a general definition. It retains some value in respect of signals from ‘spontaneous reports’, but it fails to include signals from published series or from examination of health care records, laboratory experiments, or from clinical trials or epidemiological studies. ‘Incompletely documented previously’ is also a statement which requires interpretation. A single definition of a Signal is very challenging, because of the different types of information that might constitute a signal in different contexts. A basic difficulty is: what is new? And to whom? Aronson and Hauben\(^8\) considered all definitions they could find and then produced a new one:

“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifiable and, when necessary, remedial actions.”

Edwards and Lindquist in, ‘First catch your signal’, took a different approach giving a more descriptive view of what a signal means and some practical advice on an approach to signal management.

The latest CIOMS monograph – CIOMS VIII – recently published gives a good deal of information about current thinking on signal management. It is a lengthy document, but it has an authoritative section on data mining in the context of signal detection.

**Serious adverse event or reaction**

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death or
- requires inpatient hospitalisation or prolongation of existing hospitalisation or
- results in persistent or significant disability/incapacity or
- is life-threatening

To ensure no confusion or misunderstanding of 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.

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(such as severe headache). Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligation.

This definition is used almost globally. One comment is important: the terms ‘life threatening’ and ‘requires inpatient hospitalisation’ are value judgement and context dependent, respectively. It is particularly important to reflect that whether or not a patient is admitted to hospital or not will vary from situation to situation.

In addition to the glossary of terms UMC has compiled a list of useful acronyms often used in pharmacovigilance (WHO-UMC – Public Services – Pharmacovigilance – Definitions – Abbreviations and Acronyms)
7 Relationship/ causality assessment

7.1 General considerations
The establishment of relationship between medicine intake and the occurrence of adverse events is an important activity in pharmacovigilance. It is important to consider what is meant by a ‘causal effect’. In pharmacovigilance there is rarely, if ever, a 100% guarantee that A causes B. Clinical events related to medicines may have several other causes which may be more or less likely than drugs, both in an individual case and in epidemiological studies.

The determination of causality in an individual case is quite different from the consideration of probabilities in an epidemiological study.

In a single case the logic is clinical diagnosis, considering all the factors in that case.

In epidemiology the starting point is whether the relationship between A and B has a greater probability than occurring just by chance (refuting the null hypothesis; that it did occur by chance). Usually it is accepted that a greater than 95% probability of not occurring by chance (p<0.05 of a chance relationship) is statistically significant: that a strong relationship exists.

Not being due to chance does not necessarily mean that a relationship between A and B is causal (it might be like cars and wheels which are usually related to one another, but one does not cause the other!). Neither does a study which does not show a statistically significant relationship rule out a rare causal effect: it may be that the study is too small, because other causes are much more frequent or for other more technical reasons.

For further reading see:


See also:


Some of the above also relate to signal finding, but the two topics are very much related.

Sir Austin Bradford Hill’s arguments for attributing causality are very important and are reproduced from his original paper below. It will be clear that you need good information to consider his points. Data quality is all important in any causality assessment. You are encouraged to read Bradford Hill’s original txt at: ^Hill, Austin Bradford (1965), “The Environment and Disease: Association or Causation?”, Proceedings of the Royal Society of Medicine, 58, 295-300.

**The Bradford-Hill criteria:**

These are summarized below, with comments relating to pharmacovigilance.

- **Strength:** A weak association does not mean that there is not causality but does weaken the case for common causality.
- **Consistency**: Consistent findings observed by different persons in different places, with different samples, strengthen the likelihood of causality.

- **Specificity**: Causality is more likely if the effect is observed in a very specific population at a specific geographic location and the disease has no other likely explanation.

- **Temporality**: The effect has to occur after the cause and, if there is an expected delay between the cause and the effect, the effect must occur after that delay.

- **Biological gradient**: A positive dose-response relationship strengthens the likelihood of a causal effect. With some interactions a negative dose response relationship may be suggestive.

- **Plausibility**: A plausible mechanism between cause and effect is an indicator of causality, but not all drug-effect mechanisms are known.

- **Coherence**: Evidence from clinical laboratory or clinical pathology increases the likelihood of causality, but the same issue applies as in point 6: such evidence may be unavailable.

- **Experiment**: Other experimental evidence such as animal studies may be supportive.

- **Analogy**: The effect of similar factors may be important, such as class effects of drugs.

### 7.2 Individual case assessment

The establishment of relationship between medicine intake and the occurrence of adverse events is an important activity in pharmacovigilance. Different national pharmacovigilance centres have different procedures for carrying out case causality assessment, driven sometimes by differing philosophies on the need for and importance of case causality assessment. The material below is reproduced from the WHO Manual “A practical handbook on the pharmacovigilance of antiretroviral medicines” authored by Dr. David Coulter, formerly Director of the Intensive Medicines Monitoring Programme in New Zealand (WHO, 2009).
7.2.1 **Background**
Establishing causality or a relationship between a drug and an adverse event involves two basic questions. These questions need to be addressed separately:

- Is there a convincing relationship between the drug and the event?
- Did the drug actually cause the event?

7.2.2 **Objective and subjective assessments**

7.2.2.1 **The objective phase**
This takes into account actual observations and establishes the relationship. Factors to be explored to establish a relationship are explained in Chapter 8.4.

7.2.2.2 **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.

7.2.3 **General understanding of causality/relationship assessment**
Establishing causality is a process which begins by examining the relationship between the drug and the event. The relationship in a single case-report can be established by checking the way in which the diagnosis has been reached with positive reasons supporting the diagnosis with the drug as a cause, and the exclusion of other possible causes. 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. 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?**

Causality for individual reports, even those with a close relationship, can seldom be established beyond doubt and our assessments are based on individual case probability, the increasing support of a case series and then controlled observational or even interventional studies.
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.

7.2.4 Factors to consider when assessing the relationship between drug and event

- 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.
- Is there any other possible cause for the event?
- Could the event be due to the illness being treated?
- Could it be due to some other co-existent disease?
- Could it be due to some other medicine being used concurrently?
- Is the duration to onset of the event plausible?
  - Is the event likely to have occurred in the time frame in question?
  - Did it occur too quickly to be related to the particular medicine, taking into account its pharmacological action?
  - 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.)

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

- some events take a long time to develop (e.g. cancer);
- some develop quickly (e.g. nausea and headache);
- allergic reactions to first-time exposure to a drug generally take around 10 days to appear. On repeat exposure they may occur immediately.
- 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: The new medicine may have caused the event or there may have been an interaction between the two drugs and the interaction caused the event.
• Did the event occur after the onset of some new illness? If so, the event may be due to the new illness.
• What is the response to withdrawal of the medicine (dechallenge)?
• Did the patient recover?
• Did the patient improve?
• Was there no change?
• Did the patient get worse?
• 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.

• What is the response to rechallenge?

Conditions for a positive rechallenge are:
  o the patient recovered on initial withdrawal;
  o the patient developed the same problem again when re-exposed to the same medicine alone, although it may be of different severity;
  o the patient recovered when the medicine was withdrawn once again;

It should be noted that it is not always safe to subject the patient to a rechallenge; If the response to rechallenge is unknown, this should be recorded.

7.2.5 Categories of relationship

The WHO International Drug Monitoring Programme (WHO-UMC – Public Services – Pharmacovigilance – Definitions – WHO-UMC Causality Assessment) uses six standard categories of relationship or causality between a drug and an adverse reaction or event. These are:

  Certain (or definite);
  Probable;
  Possible;
  Unlikely;
Unclassified (or conditional);
Unassessable (or unclassifiable).

Requirements for inclusion of an event in a specific category:

**Certain**

- The event is a specific clinical or laboratory phenomenon.
- 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.)
- 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.)
- 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.)
- 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.)

**Probable**

- The event is a specific clinical or laboratory phenomenon.
- 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.)
- 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.)
- 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.)
• Rechallenge did not occur, or the result is unknown.

Possible

• 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.)
• 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
• There might be no information on withdrawal of the medicine; and/or
• The event could be explained by concomitant disease or use of other drugs or chemicals; and/or
• There might be no information on the presence or absence of other medicines.

Death

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.

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:

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”.

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”.

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”.

**Unlikely**

- 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
- The event commenced before the first administration of the drug; and/or
- 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
- It is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved.

**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.

**Unassessable**

An event has occurred in association with a drug, but there are insufficient data to make an assessment. Some of the data may be contradictory or inconsistent. Details of the report cannot be supplemented or verified.
8  Signal identification in pharmacovigilance

8.1 Signal identification

General approach

The identification of signals in the national pharmacovigilance centre’s database, 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.

It is important to stress that new pharmacovigilance systems may have very few reports and may not be able to detect signals. It is therefore important for them to follow closely what is going on in other centres and also to rely on the WHO Pharmaceuticals Newsletter and UMC’s Signal document to keep abreast of signals that may be of importance to them. International collaboration is always key to both signal identification and signal strengthening and should be encouraged.

8.2 Definition of a signal

A signal is defined as “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

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

**8.3 Reference sources on adverse reactions**

Martindale, The Complete Drug Reference is probably the most reliable source of information in relation to established adverse reactions.

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.

Micromedex online drug reference is a reliable source of information.

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.

**8.4. Good data are essential**

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

The first reports with a “certain” or “probable” relationship are called “index cases”. 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.
Cases coded as “unclassified” or “unassessable” should not be considered in the investigation of a signal.

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.

8.5 Selection criteria for events to investigate

- There are good data.
- The event is clinically relevant.
- There have been several reports of the event that show a credible and strong relationship with the drug (certain or probable).

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

- require regulatory action;
- require advice to prescribers;
- be of scientific importance.

8.6 Methods of signal identification

- Clinical assessment of individual events
- Clinical review of collated events
- Record linkage
- Automated signal detection.

8.7 Clinical assessment of individual events

Careful, routine, standardized clinical assessment of individual reports with alertness to the possibility of a signal, offers the quickest method of identifying signals. This approach should be taken during routine review of incoming reports. 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. First, the national or global ICSR database should be checked for other similar reports or clinically related terms. Then the adverse reaction should be checked in appropriate reference sources. If there is no reference to the occurrence of the event as an adverse reaction, then the PV Centre should proceed with its investigation.

8.7.1 Clinical review of collated events

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.

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.

8.7.2 Collating the events

After assessment, individual events should each have a term applied to it that is selected from the events dictionary. Most dictionary terms e.g. MedDRA, WHO-ART are coded in such a way that clinically related events can be sorted to appear together. 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. For instance, 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.
8.7.3 Record linkage

Record linkage depends on the availability of a unique identifier for patients in the health system or in hospital records. This same identifier must also be recorded with the patient details in the cohort database, in case of cohort studies including cohort event monitoring. It can then be used as a tool to gather additional events data such as details of hospital admission.

The process of record linkage 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). When the patient records are linked in this way, it is possible to see, for example: if the patient has died and the date and cause of death; if the patient has been admitted to hospital and the diagnoses; if the patient has been diagnosed with a disease of special interest for which a register has been created.

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

8.7.4 Automated signal detection

8.7.4.1 Methods

BCPNN

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 and is freely available to WHO programme members online through the VigiSearch tool.
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.

**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.

**8.7.4.2 Usefulness**

Automated methods can strengthen a signal identified by clinical evaluation. They may identify signals that were missed during assessment of the reports and later review.

**8.7.5. General comment of signal identification**

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. PRR methods are more reliable in large databases, but are still somewhat experimental and lack reliability. All signals identified from statistical programmes (BCPNN or PRR) require subsequent clinical evaluation.

**8.8 Strengthening the signal**

**8.8.1 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:
• Reviewing other experience
• Searching for non-random patterns
• Reviewing the pharmacology
• Consulting one's expert safety review panel and other experts
• Undertaking epidemiological studies
• Communication and feedback

8.8.2. Reviewing other experience

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. Search the worldwide database of suspected adverse reactions of the WHO Collaborating Centre (UMC), available at: https://vigisearch.who-umc.org/. This search service requires login details from UMC (contact UMC at info@who-umc.org)

The IC value for a drug–event combination can often be found in the combinations database provided to National Centres by UMC.

If no reports can be found in VigiBase, ask for information held by other National Centres through the Vigimed e-mail network coordinated by UMC.

Search the literature for similar reports, using search tools such as PubMed or Micromedex. Ask the pharmaceutical company if they have received similar reports and ask for details. Were similar events identified in clinical trials? (Search the literature and/or ask the company for reports of clinical trials of the medicine)? Were similar events identified in preclinical studies? (Ask the pharmaceutical company.) Has this event, or have any similar events, been identified in post-marketing cohort event monitoring (prescription event monitoring or IMMP) studies?
8.8.3 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. Examine the following in particular:

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.

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?

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?

Sex differences

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

8.8.4 Reviewing the pharmacology

Is there a plausible pharmacological mechanism by which the medicine could cause the event? Have other drugs in the same class caused a similar problem and has a mechanism been described for the related drug(s)? 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.
8.8.5 Consulting one’s expert safety review panel and other experts

This should be done routinely in any pharmacovigilance centre when drug safety signals are identified or suspected. In addition to members of each country’s Pharmacovigilance Committee or Safety Review Panel members, the World Health Organization’s Advisory Committee on the Safety of Medicinal Products (ACSoMP) can be consulted through the WHO. Regional experts are also available in some regions of the world e.g. the European Union (EMA Pharmacovigilance Working Party).

8.8.6 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:

1. cohort studies
2. case–control studies
3. record linkage studies
4. population database studies.

8.8.7 Communication with other parties to gain more information

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

The following stakeholders can provide invaluable advice:

- Expert Safety Review Panel and/or regulatory authority
- Health practitioners
- Uppsala Monitoring Centre
- The pharmaceutical company
- Country ADR bulletin
- Letter or report to a medical journal.
9 Communication in pharmacovigilance

9.1 Introduction

Effective, skilled communications are vital in every aspect of pharmacovigilance. Without the best communications:

- We cannot motivate health professionals to report suspected harm to patients
- We cannot collect the range and quality of information we need to protect patients and save lives
- We cannot influence health professionals and help them achieve safer therapy.

The quality of communications influences every aspect of our professional (and private) lives:

- Performance and morale in all aspects of work (meetings, planning, public relations, training, internal and external relationships)
- Our reputation and effectiveness as individuals, teams and organisations

Pharmacovigilance risks becoming a sterile, bureaucratic system when the vision of patient safety is buried in clerical routine, paper shuffling and administrative preoccupation. PV should be a lively, dynamic, ambitious enterprise, with creative communications at its heart, and a determination to make a real difference to the health and welfare of the world.

What you will find on these pages

1. Basic knowledge and skills which apply to every aspect of communication in pharmacovigilance and across all professional (and many private) aspects of life
2. Guidance for a range of specific activities, projects and tasks in pharmacovigilance
9.2  Basic knowledge and skills

9.2.1 Interaction and the communications loop

A complete, effective communication is a message which

- has been tailored to its audiences
- has been sent out and received
- has had the desired effect (change or action of some kind)
- has generated feedback of some kind about the process
- has contributed to the refinement of future messages

Simple transmission of a message in one direction (usually outwards from the centre) is not a communication; it is essentially a random and irresponsible gesture with low probability of success. Communication is an interactive, reciprocal, continuous process.

In the cycle of effective communications, these are some of the questions which need asking and answering (most of these discussed below):

- Who exactly are my audiences and what are their needs?
- What are the best methods for reaching these audiences?
- How can I check that the message has been received?
- How can I find out what effect the message had?
- How can I establish some kind of useful interaction with my audiences?
- How can I learn to communicate more effectively next time?

9.2.2 Empathy

This quality is at the heart of all good communications.

Empathy is the ability to grasp, understand and feel what it is like to be someone else:

- their thoughts and priorities
- their worries and problems
- their view of the world
If we have a message for anybody at all (a child, an elderly person, doctors or pharmacists, for example), then we must know who they are, their circumstances when they receive our message, the ways in which they are likely to perceive and react to our message. They must feel that we understand them; that our communication recognises who they are.

**Example:** if we send out long, complicated forms or documents to busy doctors with queues of waiting patients, we are likely to be seen as irritating and thoughtless; ‘Don’t they have any idea how busy we are and how little time we have for this stuff?’ they might say. Our communication may fail because we have not acknowledged and taken account of the real-life situation of busy professionals; we have not shown empathy for them. Much of the material that follows has this fundamental challenge at its heart.

Empathy is essentially an act of mature emotional and imaginative reaching out. It comes from listening and observation, and, of course, from research (see below), but also from a disposition of humility: my urgent needs to communicate are secondary to, and must be determined by, my understanding of the nature of my audience and what they need.

### 9.2.3 Audiences

Every audience has different characteristics and needs. Communications must be tailored, shaped, focussed for a particular audience. It is obvious that a message for paediatricians is going to be very different from the message for the parents of sick children. But within the target group of parents, for example, there will also be many different groups with different needs; amongst them, parents who are:

- blind or partially sighted
- illiterate or semi-literate
- foreign language speakers
- literate and educated
- poorly motivated or lacking trust
Obviously printed materials are not much use for blind or partially sighted people; language which is suitable for educated people may mean nothing to those with poor literacy skills; a country’s mother tongue may be useless for substantial groups of immigrants. So, one message, in one form, delivered by one method, is likely to miss very large numbers of people.

You might think that an audience category like ‘doctor’ or ‘nurse’ would be simpler to deal with, but even here there will be large differences in the characteristics of individuals. Some of these include:

- Level of education and literacy
- Seniority and experience
- Speciality and interests
- Motivation and morale
- Working conditions
- Organisational commitment to (for example) patient safety

So, a highly motivated health professional, committed to advancing knowledge and career, will respond very differently from someone who is tired and demoralised and struggling against great pressure. They require different approaches, or approaches which implicitly acknowledge and respond to the differences.

### 9.2.4 Segmenting your audience

So, if you have a communication about new contraindications or adverse reactions relating to a medicine, for example, you have to review your entire audience, segment it, break it down, rationally and realistically:

- Who are the people we wish to reach or influence with this message?
- How many major groups are there with our audience?
- How many sub-groups within those larger groups?
- What are the differing needs of the groups and sub-groups we’ve identified?
- How many versions of the message does this analysis suggest we need?
For such a communication, we might identify:

- All health professionals
- Patients who are using the medicine now or may use it in the future
- Ministry of health
- Manufacturers
- Media

All five of those groups require a different formulation of the message (and different methods, see below), but within each of the major groups are several sub-groups who also require different versions of the message.

9.2.5 What is the common, great failing in much official communication?

It is simply that officials tend to sit in offices and transmit messages from the centre, conveying their wishes and priorities, without any serious consideration of their audiences, usually employing the ‘one size fits all’ approach. This is a largely futile waste of time, because the impact of communication is almost entirely random, instead of being researched, targeted and carefully calculated.

9.2.6 How do you find out what audiences need?

Simple in theory, but difficult to achieve: audience research. Every organisation with ambitions for success does audience research: commercial enterprises, political parties, most obviously. If they don’t know their audiences intimately, they won’t sell their products or get the vote. In PV and patient safety, we must be ambitious for success, and follow the example of those who know what they are doing.

So, what should we be doing?

- Talking, asking questions, listening continuously
- Meeting representative groups of our target audiences
- Commissioning audience research
Conducting surveys
Assessing the impact of our communications

This is profoundly relevant to spontaneous reporting systems (see below), safety warnings, information about benefit and harm - in fact, everything we do. For those who say, 'We don't have the time or resources' we have to ask if going through ineffective routines is a better use of resources than doing the job well.

This interaction with our audiences applies especially when we are planning new forms or leaflets or communications of any kind at all: test the material with people who will be receiving it (not with your colleagues or family members - they aren't reliable witnesses). Discuss, listen and take the advice you hear; shape you materials in line with what your audience tells you they will pay attention to. Such consultation also applies to the planning of communication methods.

9.2.7 Methods

In the twenty-first century, the printed word is not the primary medium through which the world’s population gets its information or forms its opinions. Yet, in regulation and PV we are still highly dependent on the printed word, thus dramatically reducing the potential impact of our communications.

When we know our audiences intimately, we shall have a very clear idea of the media which will be most accessible and attractive to them. They will include:

- Mobile phone programmes and apps
- Personal digital assistants (PDAs)
- Social media (Twitter, Facebook, etc)
- Internet, emails, RSS feeds
- Professional or general interest journals or publications
- TV, radio
- Printed leaflets
- Posters
- Advertising
- Peer-to-peer activities (e.g. disease-specific organisations, village meetings)
• Colloquia or training programmes
• One-to-one detailing or consultation

And what is the most powerful way of communicating with anyone and influencing them? It is, of course, one-to-one contact. The closer one is to that individual contact (in small groups for example), then the more likely it is the communication will be successful. Generally speaking, the further one is from that individual contact (a large, remote audience, for example) the more problematic the communication is and the greater the degree of creativity and energy required to reach even a fraction of the whole audience.

Ask your audiences about their habits and preferences in communications. Take notice of what they say and follow their guidance.

9.2.8 Repetition and variety

In order to reach and influence even one small segment of an audience, we may need to use several channels, and repeat the message over a long period of time. One communication is no communication. How often, first time round, do we miss the details of something someone is telling us, or find our minds wandering when we are reading? Repetition is essential.

To reach and influence people we must be creative and varied in the methods we use and continue communicating until we are sure that the message has been effective. Even then, we need to keep reminding people of the message, because once you stop communicating, the message fades. (This is most obvious in public health campaigns, like, for example, safe sex: while a campaign is active, behaviour changes and sexually-transmitted infections fall; once it stops, behaviour reverts and infections rise again).

Repeating the same message in the same format over a long period of time results in audience weariness and inattention, of course, so the message has to be constantly
refreshed and renewed (nowhere is this more significant than in stimulating ADR reporting, see below).

9.2.9 Presentation and design

The world is full of striking, often memorable and beautiful design, being promoted through every imaginable medium. We see it in every aspect of life: advertising, furniture, clothes, magazines, logos, TV programmes, electronic gadgets, cars. Everywhere, much of the enormous investment in design is calculated to attract our attention and to influence our choices in a crazily competitive and noisy environment.

How do communications in PV and safety compare with the competing messages in this vivid and exciting environment? There is no comparison. They are generally pathetic: dull, uncreative, bureaucratic.

We need to make our messages and materials credible and visible, effective and competitive. We don't have the resources for huge investment in design consultancy or extravagant production, but we can do far, far better with little or no extra expense. Most documents and forms coming from official sources look much the same all over the world: big slabs of text or endless boxes, usually in the default typeface, designed, structured and written badly; without pictures or graphics – without flair or originality. It doesn't have to be like this.

Creative energy may be found in an existing employee or may be bought modestly from a local design house. The addition of pictures and graphics costs nothing. The internet is crammed full of advice about design for every imaginable kind of document, and beautiful samples, models, pictures and images to use. Look at how commercial companies project their message and design their forms.

How our messages are presented will have a determining effect on how they are perceived and on how much impact they have. We must pay attention to how things look and make sure they are perfect for the tastes and needs of our audiences.
There are some simple principles for making text look pleasant and readable on a page:

- Leave wide margins and plenty of white (empty) space; don’t cram everything together
- Use an attractive and appropriate typeface (font)
- Use a font size which is easy to read and does not require perfect vision or a magnifying glass (nothing less than about 12 point is really attractive or easy to read for people with normal vision)
- Use a larger font size for the priority aspects of the message (see next section) and, overall, for elderly or visually handicapped people
- Give the page structure with bold headings and sub-headings
- Use graphics, charts, illustrations or photographs where possible and appropriate
- Test your ideas and materials with your specific audiences

9.2.10 Structure, content and language

Many official communications, no less in PV than in other areas, are too dense, long and complicated. The main point is often buried in the midst of a welter of detail, much of which may be irrelevant to most of the audience.

There are some very simple rules for making text as effective as possible:

- State the main purpose of the document in the title and first paragraph
- If you want recipients to do something (change their prescribing habits, for example) say so at the beginning
- If there are several messages (e.g. in a patient information leaflet), summarise the most important minimum briefly and clearly (‘If you read nothing else, read this’)
- Provide such supporting or explanatory detail as is absolutely essential
- Demote non-essential evidence or detail or further information to the end of the document, where those who want to read it can, but those who don’t, won’t miss out on critical information
You need to take a very sceptical view of recipients’ commitment to spending time on your communication. Assume they’ll give you a couple of minutes and make sure they get the essence of what you have to say in that very short period. If you manage to hook their attention in that period, they may spend more time – but if their first impression is negative, they may not give you even two minutes.

What may seem terribly important to you (not least, your wish to cover every possible angle of the topic) may be of little or no interest to your audience: you must ask yourself (in an act of empathy): How will my reader feel about this material and how I’m presenting it? What’s important for them?

These principles apply to almost every kind of communication you can imagine: letters, reports, warnings and advisories, emails, patient information or package inserts. Put the essential information at the head of the document (or web page) clearly, boldly and elegantly, and keep quite separate all secondary, supporting information.

### 9.2.11 Language and content

- Generally speaking, following these principles will result in good writing:
- Always prefer simple over complex language
- Avoid formality of style; try to write in a way which is natural and informal
- Avoid jargon, acronyms, abbreviations wherever possible; always explain them if they are essential
- Use language appropriate for your particular audience
- Keep sentences short (12-15 words where possible)
- Keep paragraphs short (6 to 10 sentences, or less, where possible)
- Use bullet points for all kinds of lists
- Use bold headings and sub-headings which provide clear signposting for the content
- Reading your material aloud (or having someone else read it to you) is the best and most reliable test of its quality
Key points:

- Develop empathy for all your audiences; understand their priorities and needs, their tastes and their preferences through research and interaction
- Shape and tailor your communications specifically for each audience and the groups and sub-groups within it
- Test your plans and your materials with each audience
- Choose a variety of methods suitable for each audience
- Repeat your message time and time again for all audiences
- Be creative and original in your design and presentation of all communications
- Plan, structure and write your communications following simple, basic principles
10 Crisis management in pharmacovigilance

Information coming soon.
11 Resources for pharmacovigilance

The section below is intended to provide support to new pharmacovigilance centres in undertaking pharmacovigilance activities. It is not intended to be all-exhaustive and would be updated in line with contemporary trends. They are guides only and further information and support may also be obtained from WHO, UMC, other WHO Collaborating Centres for Pharmacovigilance or from other national centres.

11.1 Literature resources for pharmacovigilance

There are several literature sources for information on drug safety and pharmacovigilance. The following represent the current main English language resources available and it is important to note that there are several other non-English language publications that may be equally useful and appropriate. Several of the journal articles and the WHO and UMC publications are available free of charge either as books or as PDFs.

11.1.1 Books


11.1.2 Journals

1. **BMJ** (British Medical Journal)
2. The New England Journal of Medicine
3. The Lancet
4. JAMA (Journal of the American Medical Association)
5. Drug Safety
6. Pharmacoepidemiology and Drug Safety
7. The International Journal of Risk & Safety in Medicine
8. Reactions Weekly
9. Prescrire
10. Drug Information Journal
11. ADR Newsletters from National Centres
12. Pharmacoepidemiology & Drug Safety

11.1.3 WHO-UMC publications

1. Safer Medicines, Safer Use of Medicines, Safer Patients (leaflet)
2. Aide Memoire - For a National Strategy for Safe Drugs and Their Appropriate Use
3. WHO Policy Perspectives on Medicines no. 9 - PV: Ensuring the Safe Use of Medicines
4. Viewpoint (part 1)
5. Viewpoint (part 2)
6. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products
7. Safety Monitoring - Guidelines for Setting Up and Running a Pharmacovigilance Centre
8. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions
9. Being a Member of the WHO Programme
10. Uppsala Reports (Newsletter)
11. Vigiflow - when time is crucial (leaflet)
12. VigiSearch/VigiMine (leaflet)
13. CemFlow (leaflet)
14. SIGNAL
15. WHO Pharmaceuticals Newsletter
16. WHO Drug Information
17. WHO: Pharmaceuticals: Restrictions in Use and Availability
18. Effective Communications in Pharmacovigilance - The Erice Report
21. The Safety of Medicines in Public Health Programmes - Pharmacovigilance an Essential Tool
22. A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines
23. A practical handbook on the pharmacovigilance of antiretroviral medicines
24. WHO Guidelines on Safety Monitoring of Herbal Medicines
25. Accepted Scientific Names of Therapeutic Plants and their Synonyms
26. Herbal ATC Guide
27. Writings on Pharmacovigilance - Selected articles by David J. Finney
28. A Lifetime in Safety - Selected articles by Ed Napke
29. Promoting Safety of Medicines for Children

Note that several publications are freely available in multiple languages on the WHO and UMC websites.

### 11.1.4 Data sources

**Micromedex / Drugdex / Martindale**
A convenient and comprehensive online source of information on medicines. Users are required to register and pay a fee.
https://www.thomsonhc.com/home/dispatch/PFDefaultActionId/pf.LoginAction/ssl/true

**Natural Standard**
An authoritative web site available on herbal medicines. Users are required to register and pay a fee.
http://www.naturalstandard.com/

**The Merck Manuals - Online Medical Library**
Medical reference books including disorders, tests, diagnoses, and drugs. The manuals are produced by pharmaceutical company Merck & Co. and made available on the web for free.
http://www.merckmanuals.com/home/index.html
Anatomical Therapeutic Chemical (ATC) Classification and Codes
A classification system dividing drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. The ATC classification system is maintained by the WHO Collaborating Centre for Drug Statistics Methodology.
http://www.whocc.no/atcddd/

International Classification of Diseases (ICD-10)
A medical classification published by WHO that provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. An electronic searchable version of ICD-10 is available on the web.
http://www.who.int/classifications/apps/icd/icd10online/

Medical Dictionary for Regulatory Activities (MedDRA)
A medical event dictionary used for regulatory pharmacovigilance reporting within the ICH region (US, EU, Japan). WHO-ART, the WHO Adverse Reactions Terminology, is now mapped to MedDRA. The MedDRA website provides detailed information on MedDRA and MedDRA training courses.
http://www.meddramsso.com

P450 Drug Interaction Table
A table available online which contains lists of drugs under the designation of specific cytochrome P450 isoforms. This is a useful resource when researching possible interactions that are the result of competition for, or effects on the human cytochrome P450 system.
http://medicine.iupui.edu/flockhart/table.htm

WHO Model List of Essential Medicines
The WHO has published a model list of essential medicines giving guidance on the minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The model list is intended to
serve as a guide for the development of national lists, taking into consideration local priorities.


**The International Pharmacopoeia**

The International Pharmacopoeia is published by WHO with the aim of achieving global uniformity of quality specifications for selected pharmaceutical products, excipients, and dosage forms.

Priority is given to drugs included in the WHO Model List of Essential Drugs and to drugs important for WHO health programmes which may not be included in other pharmacopoeias, e.g. new antimalarials.


**European Pharmacopoeia**

The European Pharmacopoeia lists active substances and excipients used to prepare pharmaceutical products in Europe. It includes more than 2000 specific and general monographs, including various chemical substances, antibiotics, biological substances; The European Pharmacopoeia is published by the European Directorate for the Quality of Medicines (EDQM). It is available in printed, electronic and online versions.


**United States Pharmacopeia - National Formulary (USP-NF)**

The official pharmacopoeia of the United States, published dually with the National Formulary as the USP-NF.

http://www.usp.org/

**British National Formulary (BNF)**

A medical and pharmaceutical reference containing information and advice on
medicines available on the British National Health Service (NHS).
http://bnf.org/bnf/

**VigiSearch/ VigiMine**
A web based search interface for accessing ICSRs stored in the VigiBase database, provided by UMC to member countries of the WHO Programme for International Drug Monitoring. VigiMine is an analytical tool within VigiSearch with statistics for all reported drug-ADR combinations in VigiBase. The main features include the disproportionality measure (IC value) stratified in different ways and useful filter capabilities.

UMC is currently developing a new analytical tool, VigiLyze, which will replace VigiSearch/VigiMine. For the latest information, please check the UMC web site.
https://vigisearch.who-umc.org/login.asp

**Vigimed**

An online communication and conferencing facility for fast communication and discussion of topical pharmacovigilance issues, exclusive to member countries of the WHO Programme for International Drug Monitoring. Please contact info@who-umc.org for a personal user account.

https://collaboration.who-umc.org

**11.1.5 Scientific article providers**

**HINARI (WHO)**
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

**PubMed/ Medline**
A comprehensive literature resource for articles published in medical journals, provided
by the National Center for Biotechnology Information (NCBI) - part of the United States National Library of Medicine (NLM). Abstracts are available free.

The NCBI also provides access to a list of journal abbreviations, which is essential useful resource for compiling literature references and checking the details of journals referred to in articles in the literature.

**Current Contents Connect**
A database that provides online access to complete tables of contents, bibliographic information, and abstracts from a large number of scientific journals and evaluated websites. The service is fee based.

http://thomsonreuters.com/products_services/science/science_products/a-z/current_contents_connect/

**Ingenta Connect**
A website providing a wide range of academic and professional research articles from many different publishers. Access to the full text of electronic articles is made available through online purchase of individual articles, or through subscriptions to publications.
http://www.ingentaconnect.com/

**AdisOnline**
A website providing access to Adis Journals, including Drug Safety and Reactions, which both have a pharmacovigilance focus. Adis also publish journals in the areas of clinical pharmacology, health economics, biotechnology and specialized therapy areas. The service is fee based. National pharmacovigilance centres in the WHO Programme for International Drug Monitoring are offered Reactions at a reduced price, and
individual members of the International Society of Pharmacovigilance, ISoP, have a discount on subscriptions of Drug Safety. For more information, please contact subs@adis.co.nz and administration@isoponline.org, respectively.

**Embase**
An abstracts and index database that provides online access to a wide range of biomedical journals. All Medline records produced by the NLM are included. The service is fee based.

http://www.embase.com/

**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/

**11.1.6 Selection of scientific articles**
Direct links to articles written by UMC staff and published in Drug Safety are available from the UMC website by kind permission from Adis publishers.

**Signal detection - data mining**


**General pharmacovigilance**
http://apps.who.int/medicinedocs/en/m/abstract/Js18771en/


Definitions


Incidence and prevention
Jonsson AK, Hakkarainen KM, Spigset O, Druid H, Hiselius A, Hagg S. Preventable drug related mortality in a Swedish population. Pharmacoepidemiology and Drug Safety,


**ADR reporting**


**Consumer reporting**


**Data quality management**


**Causality assessment**

**Signal detection - data mining**


**Risk management**


Communication


Patient safety - medication errors


Edwards IR. The WHO World Alliance for Patient Safety: a new challenge or an old one

Counterfeit medicines

Public health programmes


11.2 Human resources for pharmacovigilance including recruitment procedures

Information coming soon.
11.3 Template for pharmacovigilance activities

Information coming soon.
11.4 IT Equipment for pharmacovigilance including software and hardware

Information coming soon.
11.5 Draft time-table for initial workshop on pharmacovigilance

Information coming soon.
11.6 Communication flowchart

Information coming soon.
11.7 Financial issues involved in pharmacovigilance

The importance of guaranteed financial resources for undertaking pharmacovigilance activities in each country cannot be overstated. This may be part of the overall budget of the Ministry of Health or the National Drug Regulatory Authority. It may be possible for national centres to obtain funding for targeted research especially in the area of the safety monitoring of medicines and vaccines of public health importance in the country or region. The following budgetary issues highlight budget lines that should be considered and these are intended mainly as a guide to assist countries. It should be modified and used appropriately.
11.7.1 Budget for setting up a sample standard spontaneous reporting system

Information coming soon.
11.7.2 Budget for a sample cohort event monitoring programme

Information coming soon.
11.7.3 Other budgetary considerations

Information coming soon.
12 Organizations, societies and regulators

WHO Headquarters
A great deal of information is available here, including access to WHO publications.
www.who.int/

EMP/QSM (the Pharmacovigilance “department” of WHO)

HIV Programme, WHO
www.who.int/hiv/topics/pharmacovigilance/en/index.html
www.who.int/entity/hiv/pub/toolkits/3-2-8_Pharmacovigilance

Global Malaria Programme, WHO
www.who.int/gmp

Tuberculosis Programme, WHO
www.who.int/tb/en/
www.stoptb.org/

The Global Fund Against AIDS, Tuberculosis and Malaria (The Global Fund)
Financing mechanism for the three killer diseases. The Global Fund works in a transparent way which involves all stakeholders. It is run by an international multi-stakeholder governing board.
www.theglobalfund.org

The Bill & Melinda Gates Foundation (Gates Foundation)
Works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people’s health and giving them the chance to lift themselves out of hunger and extreme poverty.
www.gatesfoundation.org

The Roll Back Malaria Partnership
The RBM Partnership is the global framework to implement coordinated action against malaria. The website is an excellent resource for all things malaria.
www.rollbackmalaria.org
WHO Collaborating Centre for International Drug Monitoring: Uppsala Monitoring Centre (UMC)
This site provides very useful information about practical pharmacovigilance including definitions and advice on pharmacovigilance policy.
www.who-umc.org

WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana
The WHO-CC in Accra, Ghana works very closely with UMC and WHO and was set up to assist in particular countries in Africa. It provides training and advocacy in pharmacovigilance and distributes materials from WHO and UMC to countries who request it. The Centre is very closely aligned to Uppsala Monitoring Centre (Africa), UMC-A, which provides access to the resources and tools of UMC in Sweden.
www.pvafrica.org

The WHO Collaborating Centre for Pharmacovigilance, Morocco
The WHO-CC in Rabat, Morocco conducts and supports regional and national pharmacovigilance training courses for Francophone, Eastern Mediterranean and Arabic countries. It supports WHO normative functions related to pharmacovigilance and patient safety
www.capm.ma/sources_site_capm/pv_site_capm/pharmacovigilance_site_capm.htm

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 Pharmaceutical Federation (FIP)
Founded in 1912, the International Pharmaceutical Federation (FIP) is the global federation of national associations of pharmacists and pharmaceutical scientists and is
in official relations with the World Health Organization (WHO).

www.fip.org/

**Drug Information Association (DIA)**

DIA is a neutral, non-profit, global, professional association of nearly 18,000 members who work in every facet of the discovery, development, and life cycle management of pharmaceuticals, medical devices, and related products.

www.diahome.org/DIAHome/Home.aspx

**Drug Safety Research Unit (DSRU)**

The Drug Safety Research Unit (DSRU) is a leading independent academic research organisation internationally renowned for its work in Prescription Event Monitoring (PEM), Drug Safety and Educational Activities for more than two decades.

www.dsru.org/

**Management Sciences for Health (MSH)**

Management Sciences for Health, Inc. (MSH) is a private, non-profit educational and scientific organization working to close the gap between knowledge and action in public health.

www.msh.org/projects/sps/Pharmaceutical-Management/Pharmacovigilance.cfm

**European Medicines Agency (EMA)**

This is a useful resource on product information, current issues and regulatory actions.

www.ema.europa.eu

**European Commission (EC)**

This is the place to go to learn about the EU pharmacovigilance system.


**European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a project led by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. Its goal is to further strengthen the post-authorisation monitoring of medicinal products in Europe.

www.encepp.eu/
The Brighton Collaboration
The Brighton Collaboration website provides information on vaccine safety and is the leading source for standardized case definitions of adverse events following immunization.
www.brightoncollaboration.org

Institute for Safe Medication Practices (ISMP)
The Institute for Safe Medication Practices (ISMP) is a non-profit organization devoted entirely to medication error prevention and safe medication use. The organization is known and respected worldwide as the premier resource for impartial, timely, and accurate medication safety information.
www.ismp.org/

Food and Drug Administration (FDA), USA
This is a useful resource on product information, current issues and regulatory actions.
www.fda.gov/

Medicines and Healthcare Products Regulatory Agency (MHRA), UK
This is a useful resource containing information and several documents targeted mainly at UK practitioners but nonetheless very useful for other countries.
www.mhra.gov.uk

New Zealand Medicines and Medical Devices Safety Authority (Medsafe)
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.
www.medsafe.govt.nz/

Netherlands Pharmacovigilance Centre (Lareb)
This website provides access to the database of the Netherlands Pharmacovigilance Centre as well as signals generated by Lareb. Information is available in either Dutch or English.
www.lareb.nl

French Pharmacovigilance Centre (afssaps)
www.afssaps.fr/ (French only!)
Council for International Organizations of Medical Sciences (CIOMS)
CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO. It publishes several standardized materials on pharmacovigilance. The CIOMS website also the standard “CIOMS ADR Reporting Form” that several pharmacovigilance have utilized to provide the content for designing their own ADR reporting forms.
www.cioms.ch

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. Detailed information on ICH guidelines and requirements are available here.
www.ich.org

Rapid Pharmacovigilance Implementation in Developing Countries (RaPID)
The RaPID program, a consortium of the leading organizations in pharmacovigilance, can help develop a short- and a long-term solution. The short-term solution could be implemented within 90 days, while the long-term solution, to build institutional capacity at the country level will take 3-5 years.
www.rapidpharmacovigilance.org/
13 Technical/financial assistance and training course providers

Several organisations are involved in providing technical assistance in pharmacovigilance to countries, donor organisations and the pharmaceutical industry. The list provided below is restricted to those organisations whose activities are aimed primarily to providing technical assistance to governments, organisations and centres in resource-limited settings and excludes those whose activities are aimed solely at the pharmaceutical industry. They are divided into Collaborating Centres, Financing Entities, Technical Agencies, Academic/Research Institutions and Consultants though the distinctions may be arbitrary in that some financing entities may directly or indirectly also provide direct technical assistance.

13.1 WHO collaborating centres

Uppsala Monitoring Centre (UMC), WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
www.who-umc.org

WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Medical School, Accra, Ghana
www.pvafrica.org

WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway
www.whocc.no

The WHO Collaborating Centre for Pharmacovigilance, Rabat, Morocco
www.capm.ma/sources_site_capm/pv_site_capm/pharmacovigilance_site_capm.htm
13.2 Financing entities

The Global Fund Against AIDS, Tuberculosis and Malaria
www.theglobalfund.org

The Bill & Melinda Gates Foundation
www.gatesfoundation.org

The World Bank
www.worldbank.org

The European Commission
http://ec.europa.eu/index_en.htm

The United States Agency for International Development (USAID)
www.usaid.gov

The Global Alliance for Vaccines and Immunization
www.gavialliance.org

UNITAID
www.unitaid.eu

The Roll Back Malaria Partnership
www.rollbackmalaria.org

13.3 Technical agencies

Management Sciences for Health, Arlington, Virginia, USA
www.msh.org

University of Washington, Department of Epidemiology, USA

Clinton Health Access Initiative
www.clintonfoundation.org
13.4 Pharmacovigilance training course providers

WHO Headquarters
www.who.int/

WHO-CC for International Drug Monitoring (UMC)
www.who-umc.org

WHO-CC for Advocacy & Training in Pharmacovigilance / UMC-Africa (UMC-A)
www.pvafrica.org

WHO-CC for Pharmacovigilance
www.capm.ma/sources_site_capm/pv_site_capm/pharmacovigilance_site_capm.htm

Drug Safety Research Unit (DSRU)
www.dsru.org/

International Society of Pharmacovigilance (ISoP)
www.isoponline.org

International Society for Pharmacoepidemiology (ISPE)
www.pharmacoepi.org

Drug Information Association (DIA)
www.diahome.org/DIAHome/Home.aspx

European Medicines Agency (EMA)
www.ema.europa.eu

Eu2P (European Consortium)
www.eu2p.org/
International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
www.ich.org

London School of Hygiene and Tropical Medicine (LSHTM)
www.lshtm.ac.uk/

Swiss Tropical and Public Health Institute (Swiss TPH)
www.swisstph.ch/

Spanish Medicines Agency
www.aemps.gob.es/vigilancia/medicamentosUsoHumano/home.htm

Medicines and Healthcare products Regulatory Agency (MHRA, UK)
www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/pharmacovigilancelearningmodule/index.htm

MedEffect (Health Canada)

The Medicines Transparency Alliance (MeTA, Philippines)
www.metaphilippines.org.ph/index.php?option=com_content&view=article&id=174&Itemid=65 (go to section D. at the bottom of the website)

Empower School of Health (India)
www.empower.net.in/index.php

13.5 Universities offering pharmacovigilance related courses

- Hertfordshire, UK
- McGill, Canada
- Barcelona, Spain
- Catalan Institute of Pharmacology, Spain
- Bordeaux, France
- Verona, Italy
- Boston, USA
- Temple, USA
- Rotterdam/Utrecht, The Netherlands
- Groningen, The Netherlands
- Karolinska Institute, Sweden
- Uppsala (in collaboration with UMC), Sweden

### 13.6 Consultants

The World Health Organisation through its programme for International Drug Monitoring and in collaboration with Uppsala Monitoring Centre has since 2007 been developing a pool of pharmacovigilance consultants in Africa. These are professionals from Africa who have been provided extensive training by WHO and UMC. These consultants have now been constituted into what is informally referred to as PVSF i.e. "Pharmacovigilance Sans Frontières" or "pharmacovigilance without borders". The list of those trained and their curriculum vitae can be obtained from either WHO (pals@who.int) or UMC (info@who-umc.org).
14 Monitoring and evaluation in pharmacovigilance including pharmacovigilance indicators

There is a need for a globally acceptable monitoring and evaluation format for pharmacovigilance including pharmacovigilance indicators to permit all stakeholders to be able to assess the capacity, functioning and progress of any pharmacovigilance system. The World Health Organization through its Advisory Committee on the Safety of Medicinal Products (ACSoMP) has been developing a new set of Pharmacovigilance Indicators as part of its normative work. The final version is being discussed with various stakeholders and would be publicly available in the first half of 2012.

A comprehensive Indicator-based Pharmacovigilance Assessment Tool (IPAT) has been produced by the USAID-supported Strengthening Pharmaceutical Systems Programme implemented by Management Sciences for Health, USA. The full document can be downloaded using this link.
15 How to set up a Global Fund application for pharmacovigilance

Technical guidance notes for Global Fund HIV proposals can be viewed at the following link:

16 Disease-specific toolkits

1.0 Malaria

1.1 Brief points on malaria

- Malaria is an infectious disease caused by microorganisms of the genus Plasmodium and is prevalent in tropical and sub-tropical parts of the world.

- Humans are usually infected by four Plasmodium species namely P. falciparum, P. vivax, P. ovale and P. malariae.

- Mixed infections are not uncommon, though underestimated by routine microscopy, and occasional infections with monkey malaria parasites, such as P. knowlesi, are known to occur\(^\text{10}\).

- The parasite is carried to humans through a very effective vector, the female Anopheles mosquito.

- The distribution of these mosquitoes is closely related to the ecology of an area.

- Normally, adult mosquitoes rest during the day inside human habitats and emerge to feed at night, during which feeding malaria parasites are transferred from the salivary glands of these mosquitoes to the human blood stream.
  
  o Disease control strategies have targeted both mosquitoes and the parasite using insecticides and medicines respectively e.g. Permethrin- and alphacypermethrin-treated bed nets and curtains.

Malaria burden

- Malaria is an important cause of death and illness in children and adults in endemic countries\(^\text{11}\) with mortality, estimated at about two (2) million people per year\(^\text{12}\).

• Of these deaths, the overwhelming majority is among children aged 5 years or younger in rural sub-Saharan Africa\textsuperscript{13},

**Symptoms of malaria**

• Typical symptoms of malaria include headache, lassitude, fatigue, abdominal discomfort and muscle and joint aches; followed by fever, chills, perspiration, loss of appetite, vomiting and worsening malaise. These symptoms usually appear between 10 and 15 days after an infective mosquito bite.

• The first symptoms are non-specific and similar to those of minor systemic viral illnesses. Malaria is therefore frequently over-diagnosed on the basis of symptoms alone.

• Cerebral malaria, metabolic acidosis, severe anaemia, hypoglycaemia and, in adults, acute renal failure or acute pulmonary oedema may occur as a result of malaria.

• Mortality after administering treatment following cerebral malaria is 10-20\%\textsuperscript{14}.

**Diagnosis**

• Malaria is mostly diagnosed clinically based on symptoms presented by the patient. The current WHO guidelines for managing malaria strongly call for proper diagnosis using microscopy or rapid diagnostic tests, where these are available.


• Parasitological diagnosis, which is more definite, involves one of the following:
  o Microscopy involving identification of species, determination of parasite density as well as stage of parasite development
  o Rapid diagnostic tests (RDT) based on immunochromatographic techniques

  • Molecular technique: The use of Polymerase Chain Reaction (PCR)

1.2 Treatment of malaria

The Global Malaria Programme of the World Health Organization regularly publishes a comprehensive guideline for the management of malaria. The document, called Guidelines for the Treatment of Malaria, is freely available from the WHO website and can also be accessed through the link below.

The current version of the WHO Guidelines for Treating Malaria recommends the following as the first-line treatments for uncomplicated falciparum malaria: a combination of two or more antimalarial medicines with different mechanisms of action. Artemisinin Combination Therapies (ACTs) are the recommended treatments for uncomplicated falciparum malaria. The artemisinin derivative components of the combination must be given for at least three days for an optimum effect.

The following ACTs are recommended:

• artemether plus lumefantrine
• artemesunate plus amodiaquine
• artesunate plus mefloquine
• artesunate plus sulfadoxine-pyrimethamine, and
• dihydroartemisinin plus piperaquine.

Fixed-dose combinations are highly preferable to the loose individual medicines co-blistered or co-dispensed.
The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination: in areas of multidrug resistance (east Asia), artesunate plus mefloquine, or artemether plus lumefantrine or dihydroartemisinin plus piperaquine are recommended; and in other areas without multidrug resistance (mainly Africa), any of the ACTs including those containing amodiaquine or sulfadoxine-pyrimethamine may still be effective.

Artemisinin and its derivatives should not be used as monotherapy.

1.3 Pharmacovigilance of antimalarial medicines

The increasing resistance of the malaria parasite to established antimalarials like chloroquine and sulphadoxine-pyrimethamine (SP) led to the search for newer therapies to treat malaria. Currently, the global recommendation for the treatment of uncomplicated malaria is the use of use artemisinin-based combination therapies (ACTs). Artemisinin derivatives have been used for centuries in China and the Far East but they have only recently been deployed for use in ACTs and in several parts of the world. The information database on the safety of ACTs is quite thin and the safety profiles of artemisinins in particular and ACTs in general are not very well known in several populations and patient groups. There is little information on the safety of ACTs in pregnant women, children, the elderly and those with co-morbidities. The interactions between ACTs and medicines for HIV/AIDS and Tuberculosis are not known. The influence of genetic conditions like glucose-6-phosphate dehydrogenase (G6PD) deficiency and sickle cell disease on the disposition of ACTs is unknown. These factors make the need for safety monitoring of ACTs in all populations extremely urgent and overwhelming.

Each country or health system must have a PV system deployed to monitor the safety of all antimalarials. Pharmacovigilance systems for antimalarials may be initiated by National Malaria Control Programmes either alone or, preferably, in conjunction with national drug regulatory authorities and local hospitals. Whilst the system would be designed to focus on antimalarials, it should monitor the safety of all medicines since patients on antimalarials are likely to be taking other medicines concomitantly either to
treat the other symptoms of malaria (e.g. analgesics, haematinics, antibiotics) or to treat other acute or chronic conditions. The final decision on where to locate the Pharmacovigilance for Antimalarial Programme is a matter of national priority. This Toolkit provides guidance on malaria specific issues and also links the practitioner to the wider PV Toolkit which provides detailed information on all the basic aspects of setting up and running a PV system.

For countries applying for support from the Global Fund against HIV/AIDS and TB, provision has been made for specific support towards PV. Countries therefore have the opportunity to utilise the resources of the Global Fund to establish and/or strengthen their PV systems for antimalarials.

1.4 Management of adverse reactions to antimalarial medicines
Antimalarial medicines, like all other medicines, do have adverse events associated with their use. WHO discusses methods for collecting information related to adverse events and adverse reactions to antimalarial medicines in its publication "A practical handbook on the pharmacovigilance of antimalarial medicines". A basic handbook for the management of adverse reactions to antimalarials has been developed by the Centre for Tropical Clinical Pharmacology & Therapeutics of the University of Ghana Medical School with financial support from the Centres Disease Control and Prevention (CDC), the Global Fund, the World Health Organization and the National Malaria Control Programme of Ghana. The handbook can be downloaded using this link. It can be adopted and amended for use by other countries provided due acknowledgement is made.

1.5 Possible partnerships for implementation of pharmacovigilance of antimalarials
Who are potential partners and their roles in implementing pharmacovigilance of antimalarials?
The following table illustrates what could be the role of different potential partners, understanding that a mapping of partners and of their interests will be obtained during the preparation phase.
<table>
<thead>
<tr>
<th>Partner</th>
<th>Category</th>
<th>Example of Core Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Drug regulatory authorities, Policy makers and implementers</td>
<td>To provide inputs in strategy, to review proposed tools and processes and to implement Phase 1. To share lessons learned.</td>
</tr>
<tr>
<td>Patients and clients alliances</td>
<td>Main beneficiaries</td>
<td>To participate in selected PV activities.</td>
</tr>
<tr>
<td><strong>The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund)</strong></td>
<td>Financing Entity</td>
<td>To co-define with WHO the strategy, to stimulate the partnership on PV, to fund the ‘situational analysis’, to facilitate dissemination of PV guidelines, to sponsor in-country PV activities within the major Global Fund supported programmes.</td>
</tr>
<tr>
<td><strong>The World Health Organization (WHO)</strong></td>
<td>Normative and lead technical agency</td>
<td>To define the minimum PV requirements with Partners (esp. Countries), to define the PV toolkit, to coordinate technical support to 10-20 countries.</td>
</tr>
<tr>
<td><strong>The Uppsala Monitoring Centre, WHO-CC for PV, WHO-CC for Advocacy and Training in PV</strong></td>
<td>WHO collaborating centres on PV</td>
<td>To provide technical expertise in the initiative; to assist WHO in delivering high quality Technical Assistance (TA).</td>
</tr>
<tr>
<td><strong>Roll Back Malaria Partnership (RBM), Stop TB Partnership, Joint United Nations Programme on HIV/AIDS (UNAIDS)</strong></td>
<td>Partnerships to enhance collaborations between organisations</td>
<td>To participate in the coordination of the initiative, ensuring synergies and coherencies exist between disease specific PV efforts and transversal ones.</td>
</tr>
<tr>
<td><strong>Green Light</strong></td>
<td>Technical Agency</td>
<td>To participate in the definition of norms, to</td>
</tr>
<tr>
<td>Committee</td>
<td>deliver technical assistance.</td>
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<td>-----------------------------------------------</td>
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<tr>
<td><strong>UNITAID</strong></td>
<td>Technical Agency</td>
<td></td>
</tr>
<tr>
<td>To review proposed concept note, proposing upgrades, and join the effort (co-funding some specific activities) as a joint WHO/Global Fund/UNITAID initiative.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>U.S. President’s Emergency Plan for AIDS Relief (PEPFAR)</strong></td>
<td>Financing entity</td>
<td></td>
</tr>
<tr>
<td>To review proposed concept note, proposing upgrades and join the effort (co-funding activities) as a joint WHO/Global Fund/UNITAID/PEPFAR initiative, including additional PEPFAR supported countries in Phase 1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To facilitate the delivery of technical assistance by its implementing partners.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>The Bill &amp; Melinda Gates Foundation</strong></td>
<td>Financing entity</td>
<td></td>
</tr>
<tr>
<td>To join the initiative, ensuring advocacy at high level and to potentially sponsor some global level activities.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>The World Bank (WB)</strong></td>
<td>Financing entity</td>
<td></td>
</tr>
<tr>
<td>To review proposed concept note, proposing upgrades, and join the effort (co-funding activities) as a joint WHO/Global Fund/UNITAID/PEPFAR/WB initiative, including additional WB-supported countries in Phase 1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To use its advocacy power and bring the debate at the highest level, to facilitate delivery of technical assistance, to perform fund leveraging.</td>
<td></td>
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<tr>
<td><strong>European Union (EU)</strong></td>
<td>Financing entity</td>
<td></td>
</tr>
<tr>
<td>To review proposed concept note, proposing upgrades, and fund additional global activities (e.g. regional CEM).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To facilitate delivery of technical assistance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medicines for</strong></td>
<td>Technical agency</td>
<td></td>
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<tr>
<td>To facilitate the setting-up of active...</td>
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<td></td>
</tr>
<tr>
<td><strong>Organization</strong></td>
<td>Role</td>
<td>Remarks</td>
</tr>
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<td>--------------------------------------------------------------------------------</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Malaria Venture (MMV)</td>
<td>interfacing with academic institutions and pharmaceutical companies</td>
<td>surveillance processes (e.g. CEM) in some countries in collaboration with manufacturers.</td>
</tr>
<tr>
<td><strong>The Forum for Collaborative HIV Research</strong></td>
<td>Coordinating network</td>
<td>To facilitate interactions with stakeholders involved in PV, such as manufacturers.</td>
</tr>
<tr>
<td><strong>Global Alliance for Vaccination and Immunisation (GAVI)</strong></td>
<td>Financing entity</td>
<td>GAVI is already engaged in PV: Global Fund could learn from GAVI’s experience in PV, and the two organisations could, in general, synergize their PV activities.</td>
</tr>
<tr>
<td>European Medicines Agency (EMEA), Medicines and Healthcare Regulatory Agency (MHRA), Agence française de sécurité sanitaire des produits de santé (AFSSAPS)</td>
<td>Regulators and Northern PV agencies</td>
<td>To accompany (twinning/mentoring) selected countries as part of Phase 1.</td>
</tr>
<tr>
<td><strong>Clinton Health Access Initiative (CHAI)</strong></td>
<td>Technical agency interfacing with different stakeholders</td>
<td>To fund and/or co-organize and/or participate in regional workshops for Phase 1 countries.</td>
</tr>
<tr>
<td><strong>Médecins Sans Frontières (MSF)</strong></td>
<td>Technical agency with financing and direct implementation activities</td>
<td>To review proposed concept note, proposing upgrades; to provide specific support to some countries; to participate in the global advocacy for PV enhancement.</td>
</tr>
<tr>
<td>Management Sciences for Health (MSH) (under USAID funded-SPS program)</td>
<td>Technical agency</td>
<td>To accompany (mentoring) selected countries as part of Phase 1. To propose (and potentially, to test) innovative methods of notification. To share its PV tools, to co-sponsor/co-organize the PV stakeholder workshop.</td>
</tr>
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</tr>
<tr>
<td>Universities and Scientists</td>
<td>Technical experts and organisations</td>
<td>To accompany (mentoring) selected countries as part of Phase 1.</td>
</tr>
<tr>
<td>Manufacturers</td>
<td>Funder, Technical support</td>
<td>To provide inputs in strategy, to review proposed tools and processes, to provide financial and/or technical resources and/or technical advice to conduct special activities (roll-out of risk management plan in a few selected countries.)</td>
</tr>
</tbody>
</table>

**What is the Global Fund?**

The Global Fund, as an organization with the mission ‘to attract, manage and disburse additional resources through a new public/private partnership’ (hereby a ‘financing entity’), is relying on a variety of partners to successfully develop, implement and mature its strategy on PV.

In general, this Global Fund strategy on PV will be co-developed by the Global Fund and WHO with strong inputs from countries and other partners, each stakeholder taking advantage of the other’s skills. The Global Fund will propose to other Global Health Initiatives (GHI) to join and co-own this initiative, so it could become a GHI strategy on PV.

**What are the objectives of national pharmacovigilance system as supporting intervention of Affordable Medicines Facility - malaria (AMFm)?**
1. Overall objective: To develop or strengthen the national pharmacovigilance system to monitor, assess and improve the safety of ACT provided by the AMFM programme

2. Specific objectives:
   a) To monitor the risk for adverse drug reactions associated with ACT made available through the AMFM programme and supplied by
      a. The public sector,
      b. The for-profit private sector or
      c. The not-for-profit private sector (e.g. Non-governmental and faith-based organizations);
   b) To build a strategy for communication and feedback with healthcare professionals and the public about the safe use of ACT, based on information generated through the pharmacovigilance system;
   c) To monitor and assess the quality of the components of the pharmacovigilance system; and
   d) To monitor the safety of ACT in pregnancy by setting up or strengthening a pregnancy register at selected sites (where feasible).

Monitoring and evaluation will be required to determine the effectiveness of these interventions, to ensure that there is no under-treatment of severe malaria cases, delayed or non-referral of severe cases or misdiagnosis. Information and communication campaigns will be run to encourage the population to seek early treatment and to increase demand for high-quality, affordable, subsidized ACT.

What should be the strategy for pharmacovigilance of antimalarials?

A country’s pharmacovigilance strategy should take into consideration:

1. Patient factors, such as the population at risk for the disease, potential complications of treatment and treatment-seeking behaviour for fever and suspected malaria;
2. The health-care conditions in which the medicines are used, including available human and financial resources, diagnostic capacity, potential for investigating suspected adverse drug reactions, the patient referral system and existing pharmacovigilance activities;

3. The epidemiology, diagnosis and clinical manifestations of malaria; and

4. The effectiveness and safety of current antimalarial medicines and issues associated with an increased supply and use of act in the private sector.

What is the proposed operational plan?

The strategy will be defined and operationalized following a phased approach:

1. **The preparation phase** (2009 until Oct 2010) aimed at defining the overall concept of this initiative and preparing tools and processes for launching Phase 1. The key deliverables expected during this phase were: draft Global Fund strategy on PV (with inputs from Partners), PV minimum requirements, PV toolkit, Situation Analysis, PV plans for Phase 1 countries.

2. **Phase 1** (from Oct 2010 to June 2012) will implement the draft strategy on PV, using different approaches in 10-20 countries. The key deliverables expected during this phase are: strengthened PV systems in 10-20 countries; analysis of the different approaches that were used to support countries in strengthening their PV systems; guidelines to the Global Fund; guidelines to countries, and as the key deliverable based on lessons learned during Phase 1: the final Global Fund strategy on PV, to be shared with the Board in Nov 2012.

3. **The roll-out phase** (from 2013 and onward) will aim at implementing on a wide scale (i.e. across the whole Global Fund portfolio) the Global Fund strategy on PV. The key deliverables expected during this phase are: rooted within all Global Fund grants; plans to strengthen PV systems in all countries; to meet as a minimum, the WHO requirements on PV.

What are the criteria of selection for countries participating in phase 1?

Ideally, Phase 1 is taking place in a set of countries reflecting variations that exist within Global Fund portfolio (geography, diseases, size and income of the countries),
the various states of maturity of their national PV system, and corporate priorities and key initiative of the Global Fund (especially: AMFm and PMU-led initiatives). The countries will also be able to use Global Fund grant resources to support their in-country PV activities.

Thus the following criteria are used:

1. Existence of Global Fund grants with a potential PV component (i.e. PV activities described in grant application); in addition, the more grants in activity in the country, the better.

2. High level of awareness of PV reflected in Global Fund proposals (classification done according to WHO consultancy); most countries should be classified as ‘very good’, with some countries as ‘good’ and few ‘poor’.

3. Geographical representation, with a target of having 9 African countries, and 2 per each other Global Fund region (EECA, SWA, EAP, LAC, MENA).

4. Fair balance between large and small countries, with representation of some lower-up and middle income countries.

5. Representation of the three diseases in the Global Fund grants for these Phase 1 countries.

6. Participation in the AMFm; participation in PMU-led initiatives such as country profile, capacity building services (CBS), and the nascent NRA initiative (valuing countries with resources for NRA support as part of a Global Fund grant).

The ultimate selection criteria will be the willingness of the eligible countries to participate in Phase 1, understanding that the expected outcomes of phase 1 are 1- strengthened PV systems in the participating countries; 2- Analysis of the different approaches that were used to support countries in strengthening their PV systems; 3- Guidelines to the Global Fund to ensure that PV is included in grant proposal, successfully implemented at country level and adequately managed by the Secretariat; 4- Guidelines to countries so they can design and implement PV system. The final outcome of Phase 1 will be a well defined strategy on PV to be proposed to the Board for approval in April 2013.
1.6 Useful references for pharmacovigilance and malaria

Please refer to the lists of literature resources in Chapter 11.1 of the main PV Toolkit.
2.0 Human Immunodeficiency Virus (HIV)

The Copenhagen HIV Programme (CHIP), as part of the Monitoring Medicines Programme led by the World Health Organization (WHO) and Uppsala Monitoring Centre (UMC) and funded by the European Commission, has developed an HIV PV resource. This resource is available at [www.hivpv.org](http://www.hivpv.org).
3.0 Tuberculosis (TB)

Under development.
Appendices

Standard Operating Procedure for Spontaneous Reporting

Standard Operating Procedure for Cohort Event Monitoring

Glossary of Terms