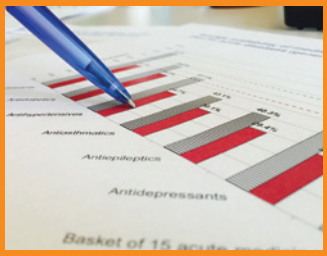
WHO PHARMACOVIGILANCE INDICATORS: A PRACTICAL MANUAL FOR THE ASSESSMENT OF PHARMACOVIGILANCE SYSTEMS



World Health Organization

WHO pharmacovigilance indicators

A practical manual for the assessment of pharmacovigilance systems

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Abbreviations

ADR	adverse drug reaction
ACSoMP	Advisory Committee on Safety of Medicinal Products
CP	core process indicator
CST	core structural indicator
HCP	health-care provider
ICSR	individual case safety report
PSUR	periodic safety update report
MAH	marketing authorization holders
QPPV	qualified person for pharmacovigilance
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

How to use this manual

This manual provides a practical method for determining the pharmacovigilance indices. It is designed to be simple and can be understood by any worker in pharmacovigilance without formal training in monitoring and evaluation. This should ensure its routine use in pharmacovigilance establishments. The current manual is published as version 1 (v1.0), to underscore its evolving nature: feedback from user groups is welcomed and will be used in developing the subsequent versions.

Pharmacovigilance as a medical discipline is crucial in preventing medicine-related adverse effects in humans, promoting patient safety, and the rational use of medicines. The indicators proposed in this manual are based on the expected functions of pharmacovigilance centres as described in the WHO Mimimum Requirements for a Functional Pharmacovigilance System *(1)* (see Annex 1 of the manual).

The structural, process and outcome or impact indicators will reflect the existence of pharmacovigilance facilities, the dynamics in the set-up, and the eventual outcomes, respectively.

The indicators are further classified as either core or complementary. The core indicators address important pharmacovigilance issues and provide information which should be readily available to enable determination of the pharmacovigilance status of the setting and allow for comparison with other settings.[1] The complementary indicators are relevant and should be determined when necessary to provide additional information in the sphere of pharmacovigilance.

To understand the indicator values, it is important to obtain the necessary background information (as shown in Annex 2), which will allow for a clear appreciation of where the data are obtained as well as providing the denominator for calculating some of the indicators. The section on description of the indicators provides information on the nature of the indicators and how to obtain them.

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[1] For the purposes of this manual, the word **setting** will be used to refer to various pharmacovigilance establishments, such as national or regional centres, hospital facilities, and public health programmes where activities relating to pharmacovigilance are in place or expected to be in place.

The indicators are expected to give a panoramic view of the pharmacovigilance landscape. Some of the indices may be measured annually or more frequently. However, for indices requiring epidemiological studies, surveys, and/or research which is likely to be cost-intensive (both financial cost and personnel time), measurements should be less frequent, in some instances every 5 years. This is especially true for indicators that measure the outcome or impact of various pharmacovigilance activities, which often require considerable resources and expertise.

This manual should be used as a tool for quality assurance and improvement: repeated measures of the indicators over time will allow an assessment of progress. It is therefore hoped that appropriate use of this practical guide will allow for a better understanding of the pharmacovigilance systems at national level, and ultimately, will lead to enhancement of pharmacovigilance systems worldwide.

In this manual, the word medicine denotes any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. However, it should be noted that the pharmacovigilance indicators described in this manual are not product-specific: they focus on structures, processes, impact and other factors, all of which are equally relevant to all product types.

This manual does not replace the WHO harmonized tool for assessing a national regulatory agency (NRA); however, a subset of indicators from this manual has been included in the NRA assessment tool to support the assessment of pharmacovigilance as an NRA deliverable. As mentioned above, this is version 1.0 of the manual and it will be revised periodically to reflect evolving use and understanding of practical issues related to the implementation of the tool.

1. Introduction

The thalidomide tragedy in the mid twentieth century triggered a chain of activities that were part of a global effort to avert a recurrence. Australia, Canada, several European countries, New Zealand and the United States of America established monitoring schemes based on reporting of suspected adverse drug reactions (ADRs). This culminated in the setting up of the WHO Programme for International Drug Monitoring *(2)*.

In the past fifty years, there has been a steady growth in the science now known as pharmacovigilance with an exponential turn in recent years. In the course of this growth, various terminologies and parameters have been introduced to enable communication and exchanges among workers in the field *(3–5)*. The need for communication on drug safety has been further endorsed in the Erice declaration.[2] However, little attention has been paid to the development of indices which will provide a baseline and allow for an assessment or quantification of the growth and performance of pharmacovigilance, which will enable comparison within and between countries, regions and facilities. Pharmacovigilance has attained the maturity and stature of a discipline that has a significant impact on patient care and public health. An effective pharmacovigilance system ensures the monitoring of medicines, their availability, and safe use. There is a need for reliable indices for the measurement, monitoring and assessment of the effectiveness of pharmacovigilance systems, including an estimation of their impact in society.

1.1 Definition of pharmacovigilance

Pharmacovigilance is defined by WHO as "the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems" *(6)*.

1.2 Scope of pharmacovigilance

The scope of pharmacovigilance has grown remarkably in recent times and is now considered to include the following domains (Figure 1):

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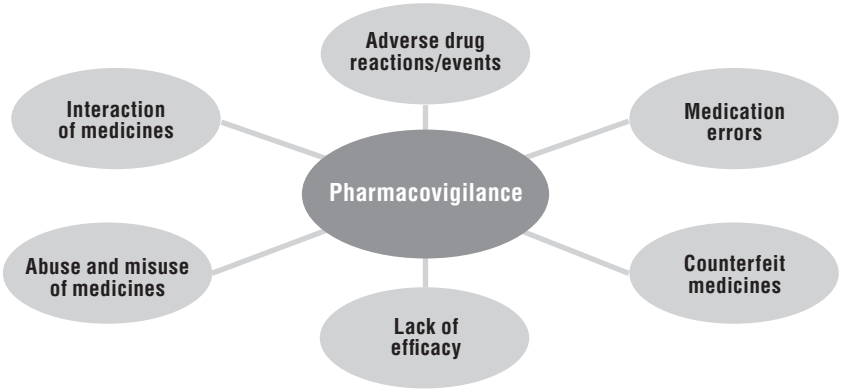
[2] More information on the Erice Declaration is available at: http://who-umc.org/graphics/24752.pdf.

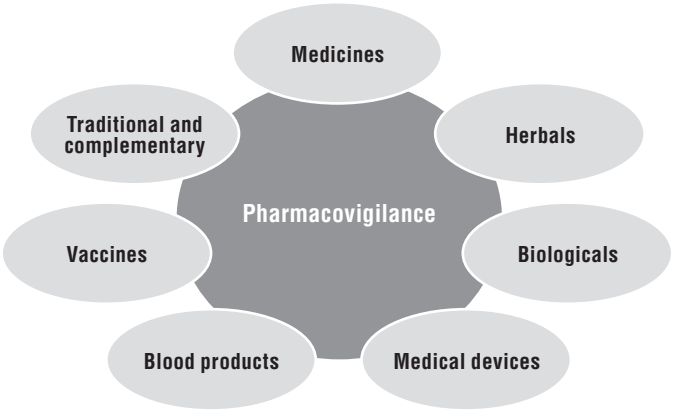
- ADRs or events
- medication errors
- counterfeit or substandard medicines
- lack of efficacy of medicines
- misuse and/or abuse of medicines
- interaction between medicines.

Figure 1. Scope of pharmacovigilance



The products under consideration go beyond conventional medicines and also include herbal medicines, other traditional and complementary products, biologicals, vaccines, blood products and possibly medical devices (Figure 2).

Figure 2. Products covered by pharmacovigilance



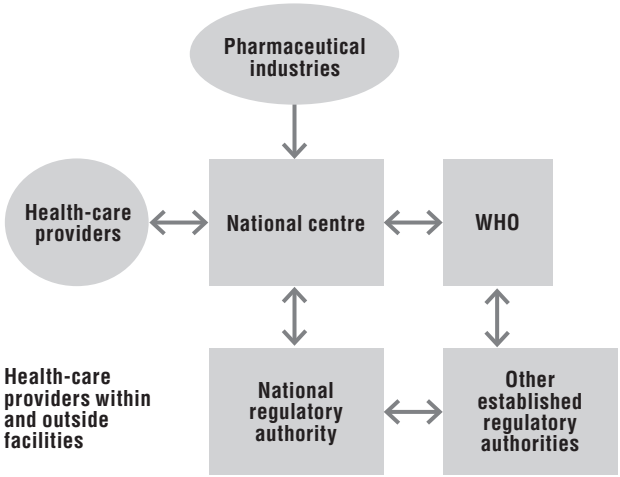
It is important to have in mind the entire scope of pharmacovigilance and spectrum of products considered during the development and use of any set of indicators to serve as tools for their monitoring and evaluation.

1.3 The pharmacovigilance system

In order to develop a set of indicators to monitor or evaluate a system it is necessary to understand its operations. The spontaneous reporting system forms the basis of global pharmacovigilance. It involves the systematic collection, collation and analysis of reports of suspected ADRs enabling detection of signals, their communication and risk management.

Figure 3 is a schematic diagram of the interactions of the pharmacovigilance system at the local, regional, national and supranational levels. At the local level, health-care providers (HCPs) and patients forward reports of suspected ADRs to appropriate regional or national centres for collation, analysis and evaluation. The manufacturing industries do the same. This information is further processed and forwarded to the WHO individual case safety report (ICSR) database – VigiBase. The national pharmacovigilance centres receive significant feedback since findings are promptly communicated to them by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden (UMC) for appropriate action. The sophistication of the operations varies from rudimentary facilities in low- and middle-income countries to the more advanced technology in resource-rich countries.

Figure 3. Diagrammatic representation of the pharmacovigilance system



2. Pharmacovigilance indicators

2.1 Definitions

Indicators are specific objective measures that allow the evaluation of the baseline situation and progress in systems and the assessment of services and interventions. Pharmacovigilance indicators are measures of inputs, processes, outputs, outcomes, and impacts of development projects, programmes or policies related to health systems and services. They provide information for measuring how well a pharmacovigilance programme is achieving its objectives.

2.2 Rationale and objectives of pharmacovigilance indicators

The indicators should measure the existence and performance of key pharmacovigilance structures and processes and be able to identify the strengths and weaknesses, as well as revealing the achievements, growth or lack of growth of the pharmacovigilance systems. They should also measure the degree of attainment of set strategic objectives.

The main objective of the pharmacovigilance indicators is to provide measures that will enable the assessment of the status of pharmacovigilance, the activities and their impact, globally at all levels of the health-care system, with a view to ensuring patient safety. The availability of this set of pharmacovigilance indicators will also provide objective indices with which to measure performance in this area. In essence, a set of indicators addressing pharmacovigilance issues will:

- provide objective measures to describe the pharmacovigilance situation in a country;
- assess pharmacovigilance activities – at the global (national), regional and health-care facility levels;
- assess capacity of (and for) pharmacovigilance at these levels;
- provide tools for supervision and monitoring of pharmacovigilance activities;
- assess progress and enable the prioritization of efforts, based on this assessment;
- enable comparison of pharmacovigilance activities between geographical regions and health facilities at a given time and at different times;

- provide tools for measuring the impact of interventions; and
- provide information for governments and other stakeholders to enable them to take appropriate action in ensuring drug safety.

2.3 Characteristics of ideal pharmacovigilance indicators

These indicators are intended to have the four important characteristics, namely they should:

- be simple to understand;
- not require great expertise to measure and interpret;
- be reproducible – irrespective of investigator;
- be specific and sensitive, so that they are able to detect pharmacovigilance problems needing attention as well as changes in the pharmacovigilance systems.

The indicators proposed are thus as SMART[3] as possible. However, as discussed later, some indicators, such as the impact or outcome indicators, can only be measured through surveys or specific studies. The effort required to conduct such surveys so as to generate useful data must be appreciated. These surveys are usually carried out periodically and are of great relevance in determining the impact of intervention(s).

2.4 Classification (type) of pharmacovigilance indicators

Prior to using the pharmacovigilance indicators it is necessary to obtain some background information (for more on background information see Annex 2). This information will define and describe the milieu where the pharmacovigilance activities are taking place and other factors likely to impact on pharmacovigilance. The information obtained will cover demographics, economics, the health-care system and the pharmaceutical scenario. This will provide the denominator for calculating most of the indicator values.

The pharmacovigilance indicators are classified into the following three groups:

- structural indicators
- process indicators
- outcome or impact indicators.

2.4.1 Structural indicators

The structural indicators assess the existence of key pharmacovigilance structures, systems and mechanisms in the setting being studied. The availability

[3] SMART: Specific, Measurable, Attainable, Relevant and Timebound.

of basic infrastructure is required to enable pharmacovigilance operations. These indicators assess the elements that give visibility to pharmacovigilance. They also assess the existence of a policy and regulatory framework which enables pharmacovigilance to operate. These indicators are essentially qualitative.

2.4.2 Process indicators

The process indicators assess the extent of pharmacovigilance activities. They focus on the constellation of activities which describe the mechanism of pharmacovigilance – the collection, collation, analysis and evaluation of ADR reports. They also consider other activities which influence those listed above. These are measures that assess directly or indirectly the extent to which the system is operating.

2.4.3 Outcome and impact indicators

The outcome and impact indicators measure the effects (results and changes) of pharmacovigilance activities. They measure the extent of realization of the pharmacovigilance objectives which, in essence, constitute ensuring patient safety.

3. The context of WHO pharmacovigilance indicators

3.1 WHO strategy for monitoring a country's pharmaceutical situation

WHO uses a three-tiered approach for monitoring a country's pharmaceutical situation *(7)*.

- Level I indicators measure the existence and performance of core national pharmaceutical structures and processes.
- Level II indicators measure key outcomes of these structures and processes in the areas of access to, and rational use of pharmaceutical products.
- Level III indicators assess specific components of the pharmaceutical sector, health system, or national medicines policy in more depth.

Consistent with this approach, the current set of pharmacovigilance indicators are categorized under Level III. Safety of medicines is an important consideration in the use of pharmaceutical products and underscores the relevance of the set of pharmacovigilance indicators.

3.2 How the WHO pharmacovigilance indicators were developed

The conceptualization of the pharmacovigilance indicators followed a meeting of pharmacovigilance experts held in Accra, Ghana in 2007. At its fifth meeting, the WHO Advisory Committee on Safety of Medicinal Products, ACSoMP, defined the principles applicable when developing a set of core and complementary indicators and recommended a process for arriving at a useful pharmacovigilance evaluation instrument *(8)*.

Further presentations, reviews and contributions were made at the meetings of the African Pharmacovigilance Consultant Group in 2008, in Accra, Ghana and in 2009, in Maputo, Mozambique. A working group at the thirty-first annual meeting of Representatives of National Centres participating in the WHO Programme for International Drug Monitoring, held in Sweden in 2008, discussed the use of indicators for measuring development and impact of pharmacovigilance in countries *(8)*. The first set of potential indicators was thus developed in a step-wise fashion, based on a clear understanding of the pharmacovigilance system: the relevance of the setting, the structures, operations and impact were all considered. A significant input into the process

indicators came from the pharmacovigilance landscape assessment study by Olsson et al. *(9)*.

The indicators identified were then presented at the thirty-second annual meeting of Representatives of National Centres participating in the WHO Programme for International Drug Monitoring held in Rabat, Morocco in November 2009 *(10)* following which the indicators were circulated to National Centres for categorization into core and complementary indicators. This was done to obtain global stakeholders' input in the further characterization and prioritization of the indicators, thus highlighting the importance, relevance and usefulness of each of the indicators in the context and settings where they would be used. The outcome of this survey was discussed at the WHO Pharmacovigilance Consultants' meeting in Lomé, Togo in August 2010. At this meeting the relevance of and need for a set of indicators for public health programmes was suggested.

The indicators were validated by a team of experts of ACSoMP.

4. Categories of WHO pharmacovigilance indicators

The two suggested categories (Core and Complementary indicators) are explained below. Each of the categories include the three types of indicators – structural, process and outcome or impact (see section 2.4). Additionally, a set of indicators have been selected to address public health programmes.

1. Core indicators (C) are those considered to be highly relevant, important and useful in characterizing pharmacovigilance.
2. Complementary indicators (T) are those additional measurements considered to be relevant and useful. They serve to further characterize the pharmacovigilance situation in the stated setting but need not be used in all instances.
3. Pharmacovigilance indicators for public health programmes: the large-scale deployment of medicines in public health programmes implies the exposure of a large number of people to medicinal products. Importantly, such a programme might entail the use of new medicines whose safety profiles have not been fully characterized or older medicines with a toxic profile. It is therefore imperative that a pharmacovigilance system is in place to ensure safe use of these medicines, thus safeguarding the health of the population. The place of a simplified set of pharmacovigilance indicators in ensuring adequate monitoring with objective measurements cannot be overemphasized. This publication describes nine pharmacovigilance indicators for public health programmes. The methods for obtaining the indices are variable and might include rigorous surveys; this, however, should not exclude them from consideration.

4.1 Core pharmacovigilance indicators

There are 27 core pharmacovigilance indicators: 10 structural, 9 process and 8 outcome or impact indicators.

4.1.1 Core structural indicators

The 10 core structural indicators (CSTs) are as follows:

CST1. Existence of a pharmacovigilance centre, department or unit with a standard accommodation

CST2. Existence of a statutory provision (national policy, legislation) for pharmacovigilance

CST3. Existence of a medicines regulatory authority or agency

CST4. Existence of any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre

CST5. The pharmacovigilance centre has human resources to carry out its functions properly

CST6. Existence of a standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

CST6a: suspected medication errors;

CST6b: suspected counterfeit/substandard medicines;

CST6c: therapeutic ineffectiveness;

CST6d: suspected misuse, abuse of and/or dependence on medicines;

CST6e: ADRs by members of the general public

CST7. A process is in place for collection, recording and analysis of ADR reports

CST8. Incorporation of pharmacovigilance into the national curriculum of the various health-care professions (includes *subset indicators*:

CST8a: for medical doctors;

CST8b: for dentists;

CST8c: for pharmacists;

CST8d: for nurses or midwives;

CST8e: for others – *to be specified*)

CST9. Existence of a newsletter, information bulletin or website for dissemination of pharmacovigilance information

CST10. Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety.

4.1.2 Core process indicators

The nine process indicators are as follows:

CP1. Total number of ADR reports received in the previous calendar year (also expressed as number of ADRs per 100 000 persons in the population)

CP2. Current total number of reports in the national, regional or local database

CP3. Percentage of total annual reports acknowledged and/or issued feedback

CP4. Percentage of total reports subjected to causality assessment in the previous calendar year

CP5. Percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous calendar year

Subset indicator CP5a: of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database

CP6. Percentage of total reports attributed to therapeutic ineffectiveness received in the previous calendar year

CP7. Percentage of reports on medication errors reported in the previous year

CP8. Percentage of registered pharmaceutical companies having a functional pharmacovigilance system

CP9. Number of active surveillance activities initiated, ongoing or completed during the past five calendar years

4.1.3 Core outcome or impact indicators

The eight outcome or impact indicators are as follows:

CO1. Number of signals detected in the past 5 years by the pharmacovigilance centre

CO2. Number of regulatory actions taken in the preceding year as a consequence of national pharmacovigilance activities includes

- CO2a: number of product label changes (variation);
- CO2b: number of safety warnings on medicines to: (i) health professionals, (ii) general public;
- CO2c: number of withdrawals of medicines;
- CO2d: number of other restrictions on use of medicines

CO3. Number of medicine-related hospital admissions per 1000 admissions

CO4. Number of medicine-related deaths per 1000 persons served by the hospital per year

CO5. Number of medicine-related deaths per 100 000 persons in the population

CO6. Average cost (US$) of treatment of medicine-related illness

CO7. Average duration (days) of medicine-related extension of hospital stay

CO8. Average cost (US$) of medicine-related hospitalization

4.2 Complementary indicators

There are 36 complementary indicators: 11 structural, 13 process and 12 outcome or impact

4.2.1 Complementary structural indicators

The 11 complementary structural indicators are as follows:

ST1. Existence of a dedicated computer for pharmacovigilance activities

ST2. Existence of a source of data on consumption and prescription of medicines

ST3. Existence of functioning and accessible communication facilities in the pharmacovigilance centre

ST4. Existence of a library or other reference source for drug safety information

ST5. Existence of a computerized case-report management system

ST6. Existence of a programme (including a laboratory) for monitoring the quality of pharmaceutical products

Subset indicator ST6a: The programme (including a laboratory) for monitoring the quality of pharmaceutical products collaborates with the pharmacovigilance programme

ST7. Existence of an essential medicines list which is in use

ST8. Systematic consideration of pharmacovigilance data when developing the main standard treatment guidelines

ST9. The pharmacovigilance centre organizes training courses

ST9a: for health professionals;

ST9b: for the general public

ST10. Availability of web-based pharmacovigilance training tools

ST10a: for health professionals;

ST10b: for the general public

ST11. Existence of requirements mandating market authorization holders to submit periodic safety update reports

4.2.2 Complementary process indicators

The 13 complementary process indicators are as follows:

- P1. Percentage of health-care facilities with a functional pharmacovigilance unit (i.e. submitting ≥ 10 reports to the pharmacovigilance centre) in the previous year
- P2. Percentage of total reports sent in the previous year by the different stakeholders includes
  - P2a: percentage of total reports sent by medical doctors;
  - P2b: by dentists;
  - P2c: by pharmacists;
  - P2d: by nurses or midwives;
  - P2e: by the general public;
  - P2f: by manufacturers
- P3. Total number of reports received per million population per year
- P4. Average number of reports per number of health-care providers per year includes
  - P4a: by medical doctors;
  - P4b: by dentists;
  - P4c: by pharmacists;
  - P4d: by nurses or midwives
- P5. Percentage of health-care providers aware of and knowledgeable about ADRs per facility
- P6. Percentage of patients leaving a health facility aware of ADRs in general
- P7. Number of face-to-face training sessions in pharmacovigilance organized in the previous year
  - P7a: for health professionals;
  - P7b: for the general public
- P8. Number of individuals who received face-to-face training in pharmacovigilance in the previous year
  - P8a: number of health professionals trained in the previous year;
  - P8b: number of individuals from the general public trained in the previous year
- P9. Total number of national reports for a specific product per volume of sales of that product in the country (product specific) from the industry

P10. Number of registered products with a pharmacovigilance plan and/or a risk management strategy among the marketing authorization holders in the country

Subset indicator P10a: Percentage of registered products with a pharmacovigilance plan and/or a risk management strategy from the market authorization holders in the country

P11. Percentage of market authorization holders who submit periodic safety update reports to the regulatory authority as stipulated in the country

P12. Number of products voluntarily withdrawn by market authorization holders because of safety concerns in the previous year

Subset indicator P12a: Number of summaries of product characteristics (SPCs) updated by market authorization holders because of safety concerns in the previous year

P13. Number of reports from each registered pharmaceutical company received by the pharmacovigilance centre in the previous year

4.2.3 Complementary outcome or impact indicators

The 12 outcome or impact indicators are as follows:

O1. Percentage of preventable ADRs reported in the previous year out of the total number of ADRs reported

O2. Number of medicines-related congenital malformations per 100 000 births

O3. Number of medicines found to be possibly associated with congenital malformations in the past 5 years

O4. Percentage of medicines in the pharmaceutical market that are counterfeit/substandard

O5. Number of patients affected by a medication error in hospital per 1000 admissions in the previous year

O6. Average work or schooldays lost due to drug-related problems

O7. Cost savings (US$) attributed to pharmacovigilance activities

O8. Health budget impact (annual and over time) attributed to pharmacovigilance activity

Rational use of medicines

O9. Average number of medicines per prescription

O10. Percentage of prescriptions with medicines exceeding manufacturer's recommended dose

O11. Percentage of prescription forms prescribing medicines with potential for interaction

O12. Percentage of patients receiving information on the use of their medicines and on potential ADRs associated with those medicines

4.3 Indicators for public health programmes

There are nine pharmacovigilance indicators for public health programmes.

PH1. Pharmacovigilance activities included within the operational document of the public health programme

PH2. All main treatment guidelines or protocols in use within the public health programme systematically consider pharmacovigilance

PH3. Existence of standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

PH3a: suspected medication errors;

PH3b: suspected counterfeit/substandard medicines;

PH3c: therapeutic ineffectiveness;

PH3d: suspected misuse, abuse of and/or dependence on medicines

PH4. Total number of ADR reports collected within the public health programme in the previous year

PH5. Total number of ADR reports per 1000 individuals exposed to medicines in the public health programme in the previous year

PH6. Total number of reports on therapeutic ineffectiveness in the previous year

PH7. Percentage of completed reports submitted to the national pharmacovigilance centre in the previous year

Subset indicator: PH7a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database

PH8. Number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the public health programme in the previous year

PH9. Number of medicine-related deaths per 1000 individuals exposed to medicines in the public health programme in the previous year

5. Data sources

The data for the indicators should be obtainable from the following sources:

- databases – national database (census figures, registers), pharmaceutical databases (e.g. figures on sales, prescription, consumption)
- national pharmacovigilance centres
- hospital or clinic records
- surveys.

The indicator data are either qualitative or quantitative. The data for the structural indicators are mainly qualitative whereas those for process and outcome or impact indicators are quantitative.

In some instances it may be necessary to carry out specific surveys to generate the data, particularly for the impact indicators. Such surveys may require specific expertise, may be time- and resource-intensive, and would need to be closely coordinated with relevant institutions (such as the ministry of health, national office of health statistics, universities, and research agencies).

5.1 Indicator format

For each indicator the following elements, which characterize the indicator, will be stated.

Definition

- What is the content of the indicator? What is its numerator and its denominator?

Description and uses

- What will it measure?
- Why is it important?
- What is the scope of the indicator?
- How can the results be interpreted?

Sources and methods of data collection and indicator calculation

- What are the main sources and methods of data collection?
- How should the indicator be calculated?

Limitations

- What are the limitations of the indicator?

6. Description of core indicators

6.1 Core structural indicators

CST1

Existence of a pharmacovigilance centre, department or unit with a standard accommodation

Definition

The presence in the setting – national, regional, zonal, health facility – of a space specifically dedicated to pharmacovigilance activities.

Description and uses

The existence of a space for pharmacovigilance activity provides the necessary visibility for pharmacovigilance and a meeting point for interaction. It also indicates political and administrative commitment towards achieving pharmacovigilance objectives.

The accommodation provided should have the basic office equipment and facilities required to receive, analyse and transmit ICSRs and provide the necessary feedback as well as to enable pharmacovigilance communication.

Sources and methods of data collection and indicator calculation

The information is qualitative and the presence or absence of accommodation is noted. The source of information should be the ministry of health of the country concerned, since it serves a supervisory role for all matters of health. The pharmacovigilance centre must be recognized, and/or accredited by the ministry of health.

Limitations

The dichotomous response expected does not account for non-functional pharmacovigilance centres or those at developmental non-commissioned stages.

CST2

Existence of a statutory provision (national policy, legislation) for pharmacovigilance

Definition

The existence of a statutory provision refers to the enabling instrument, such as a national policy document or a legislative provision enacted by the appropriate arm of government to support pharmacovigilance activities in the setting.

Description and uses

The instrument should spell out specifics empowering the appropriate authorities to carry out pharmacovigilance activities with well-defined roles and responsibilities.

The existence of this instrument underscores the commitment of the government of the setting to ensuring the safe use of medicines. It empowers the operators to carry out their work with conviction.

Sources and methods of data collection and indicator calculation

The information is qualitative and the presence or absence is noted. The source of information should be the ministry of health of the country concerned, since it serves a supervisory role for all matters of health.

Limitations

The main limitation of enabling instruments is that their presence does not necessarily translate into effective and efficient pharmacovigilance machinery. In other words, the mere presence of an enabling instrument does not indicate a functional pharmacovigilance system. Also the existence of legislation does not imply that it is specific and comprehensive (addressing all the required aspects of pharmacovigilance), nor that it is up-to-date.

CST3

Existence of a medicines regulatory authority or agency

Definition

The existence in the setting of an organ responsible for medicines' regulation.

Description and uses

The indicator is qualitative and notes the presence or absence of a statutory regulatory agency. The presence of a regulatory agency suggests the availability of a regulatory framework for pharmaceutical products in the setting being an important stakeholder and focal point for promoting pharmacovigilance.

Sources and methods of data collection and indicator calculation

The information on the presence of a medicines regulatory agency should be obtained from the ministry of health. The information is qualitative, and the presence or absence is noted.

Limitations

The limitation of this indicator is its inability to express the functional status and effectiveness of the operations concerning pharmacovigilance.

CST4

Existence of any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre

Definition

A financial arrangement specifically for the pharmacovigilance centre refers to the provision of a regular (e.g. yearly) and sustained funding source to enable the running of the facility.

Description and uses

This indicator notes the presence or absence of a statutory budget and funding source. The availability of funding represents the possibility for the centre to carry out pharmacovigilance activities in the setting. It also signifies a gesture, the commitment and political will of the sponsors and the general importance given to pharmacovigilance.

Sources and methods of data collection and indicator calculation

The information regarding the provision for funding should be obtained from the pharmacovigilance centre. The information is qualitative, and the presence or absence is noted.

Limitations

The limitation of this indicator is that the actual budgetary allocation, or the total amount available to the centre to fund its activities, is not stated. It is therefore not possible to state whether the funding is sufficient to ensure the effective operation of the centre.

CST5

The pharmacovigilance centre has human resources to carry out its functions properly

Definition

The presence in the pharmacovigilance centre of trained staff to carry out all essential functions properly.

Description and uses

This indicator suggests the presence of human resources in the pharmacovigilance centre to take on the various duties and responsibilities expected. It provides a measure of the staff complement required for effective running of a pharmacovigilance centre.

Sources and methods of data collection and indicator calculation

The head of the pharmacovigilance centre should be requested to supply the data for this indicator.

The information obtained should include the number of staff in the centre. The number of full-time and part-time staff should be noted and represented as full-time equivalents. This information should be compared with the expected total full-time equivalents required to enable the pharmacovigilance centre to fulfil all its duties and responsibilities. The information obtained is qualitative, and the presence or absence of adequate staff is noted.

Limitations

The main limitation of this indicator is its inability to assess and state the level of expertise of the personnel and this may impact on the standards of the centre. Also, clear guidance on the required full-time equivalents may not be available.

CST6

Existence of a standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

CST6a: suspected medication errors;

CST6b: suspected counterfeit/substandard medicines;

CST6c: therapeutic ineffectiveness;

CST6d: suspected misuse, abuse of and/or dependence on medicines;

CST6e: ADRs by the general public.

Definition

This indicator relates to the use of a standard ADR reporting form with all its elements in the setting.

Uses and description

The indicator measures the presence in the setting of a data collection tool for pharmacovigilance operations. It suggests that the requisite tool for collecting critical information on a suspected case of medicine-related harm has been fully integrated into the pharmacovigilance system.

The reporting form should contain all elements normally required to enable causality assessment of a case based on clinical evidence.

The subset indicators (CST6a–CST6d) address whether the ADR form includes the relevant sections to allow and to encourage practitioners to report on all the domains covered by pharmacovigilance as shown in Figure 1. Subset indicator CST6e refers to the recognition of the general public as stakeholders in pharmacovigilance and it also measures the preparedness of a facility to support reporting of ADRs by the public.

Sources and methods of data collection and indicator calculation

The information should be obtained from the pharmacovigilance centre. The information obtained is qualitative, and presence or absence is noted.

Limitations

The limitation of this indicator is that it reports the presence in the system of a reporting form and does not provide information on how it is put to use. The functionality is therefore not assessed. There is no consensus regarding the elements required for the performance of an evidence-based causality assessment.

The information covered by the four subset indicators (CST6a–CST6d) may also be captured by information management tools other than the reporting forms (e.g. medical records), and the information is then sent to the pharmacovigilance centre. This can potentially lead to duplication.

CST7

A process is in place for collection, recording and analysis of ADR reports

Definition

This refers to the existence of a chain of activities relating to the handling of reports – causality assessment, feedback and submission to WHO.

Description and uses

The response is qualitative but will assess the presence of a report management process with provision for feedback, causality assessment and an electronic database. This indicator is a measure of the functionality and presence of an operational process in the pharmacovigilance centre.

Sources and methods of data collection and indicator calculation

The head of the pharmacovigilance centre should be interviewed and requested to supply the data for this indicator. A qualitative response is obtained, i.e. presence or absence of the process.

Limitations

The main limitation of this indicator is that it is a qualitative measure of the existence or non-existence of a case management system and provides no information of the process involved.

CST8

Incorporation of pharmacovigilance into the national curriculum of the various health care professions

Includes

CST8a: for medical doctors;

CST8b: for dentists;

CST8c: for pharmacists;

CST8d: for nurses or midwives;

CST8e: for others – to be specified

Definition

This indicator assesses whether pharmacovigilance has been incorporated into the national curriculum of the various health-care professions.

Description and uses

The incorporation of pharmacovigilance into the national curriculum for training health professionals suggests an early exposure to pharmacovigilance for the various categories of personnel engaged in the care of patients. This exposure sensitizes the health professionals early in their career to issues regarding the safety of medicines. It is an essential step in integrating pharmacovigilance into the health-care system. The absence of pharmacovigilance in the training curriculum suggests a lack of preparedness of the health professionals for career challenges on issues of safety of medicines.

Sources and methods of data collection and indicator calculation

The information should be obtainable from the relevant professional regulatory bodies for medical doctors, pharmacists, nurses and other allied professions on request.

The response is qualitative – yes/no for each professional category.

Limitations

The quality of the training is not captured: the main limitation of this indicator is its inability to elicit the extent of implementation.

CST9

Existence of a newsletter, information bulletin and/or website as a tool for dissemination of information on pharmacovigilance

Definition

This indicator refers to the presence of a system for the regular dissemination of information on medicines safety to health-care professionals and to the public (newsletter, and/or an information bulletin, and/or a website).

Description and uses

One of the expected functions of a national pharmacovigilance system is to provide effective communication on aspects related to safety of medicines. A clear strategy for routine communication and communication during crises is one of the minimum requirements for a functional national pharmacovigilance system.

Sources and methods of data collection and indicator calculation

The information regarding the existence of such communication tool(s) should be obtainable from the pharmacovigilance centre. The information is qualitative and the presence or absence of the tool(s) is noted.

Limitations

The quality and frequency of the communication (including the validity of its content, the relevance to the audience, the effectiveness and efficiency of the chosen media) are not assessed. This indicator does not assess the preparedness and effectiveness of the pharmacovigilance centre in communicating in the event of a crisis nor can it measure the impact of the information on professional behaviour.

CST10

Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety

Definition

This refers to the existence of a qualified committee that can provide advice and technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication.

Description and uses

The response is qualitative and indicates whether sufficient competence is accessible to the pharmacovigilance centre staff to support all the main functions of a pharmacovigilance system. A committee should be composed of a

minimum of three people with different professional backgrounds in health care and should meet regularly. On a regional or local level the function could be assumed by a drug and therapeutics committee.

Sources and methods of data collection and indicator calculation

The data should be obtainable from the pharmacovigilance centre. A qualitative response is obtained – present or absent.

Limitations

The main limitation of this indicator is that it does not measure the breadth or depth of the competencies represented in the committee, the frequency of its meetings or the relevance of its advice to the pharmacovigilance centre.

6.2 Core process indicators

CP1

Total number of ADR reports received in the last calendar year (also expressed as number per 100 000 people in the population)

Definition

This indicator states the number of ADR reports received annually by the centre. It is an indication of the volume of reports generated within the population.

Description and uses

The indicator serves to measure the pharmacovigilance activity in the setting, the awareness of ADRs and the willingness of health professionals to report.

Valid case reports should contain the four core data elements, as per ICH-E2A (11):

1. reporter
2. identifiable patient
3. suspected medicines
4. adverse reaction.

The trend of this indicator enables authorities to appreciate the measures taken to improve reporting. When expressed in relation to the population it allows for comparison between countries and within country facilities, regions or zones.

Sources and methods of data collection and indicator calculation

The main source of data is the database at the national, or other relevant, pharmacovigilance centre where reports are received and collated.

The values of this indicator are (i) absolute number of reports and (ii) number of reports per 100 000 people in the population. The latter is useful for comparative purposes.

Limitations

The quality of the documentation or relevance for signal identification will not be measured.

CP2

Current total number of reports in the national, regional or local database

Definition

This indicator refers to the current total number of reports in the relevant database.

Description and uses

The indicator is a measure of cumulative reports in the database since its inception. It is a measure of pharmacovigilance activities in the setting and the strength of the database. The size of a database, as well as its pace of growth over time (obtained from CP1), can be used for comparative purposes and provides useful information.

Sources and methods of data collection and indicator calculation

The main source of the data is the database in the relevant pharmacovigilance centre. The data are obtainable from the administrative head of the pharmacovigilance unit. The absolute total number of reports is all that is required.

Limitations

The main limitation of this indicator is that while it provides the size of the database, there is no information on the quality of reports. The rationale behind reporting trends (investigated through CP1) cannot be determined through this indicator.

CP3

Percentage of total annual reports acknowledged/issued feedback

Definition

This indicator refers to the proportion of the reports for which the reporters received some individual acknowledgement and information from the officials of the pharmacovigilance centre.

Description and uses

It is expected that in response to receiving a report, the personnel in the pharmacovigilance centre will provide an informed acknowledgement to the

reporting health-care personnel. The number of reports provided with this feedback is documented. It is a measure of the responsiveness of the centre to submitted reports.

A high percentage suggests a commendable level of response by the personnel at the pharmacovigilance centre. Low feedback rates discourage reports from health-care professionals.

Sources and methods of data collection and indicator calculation

The main source of the data is the pharmacovigilance centre, which should provide records of the number of reports provided with feedback and the total number of reports received during the one-year period. The indicator can then be calculated as follows:

$$\frac{\text{Number of reports provided with feedback during the one-year period}}{\text{Total number of reports received during the one-year period}} \times 100$$

Limitations

The limitation of this indicator is that it does not assess the quality of the contents, nor the delay in providing the feedback.

CP4

Percentage of total reports subjected to causality assessment in the previous calendar year

Definition

The indicator refers to the proportion of reports subjected to causality assessment in the last calendar year.

Description and uses

The characterization of a report and determination of its quality is carried out to a large extent during the causality assessment. It is a measure of the activities of the national centre staff and those of the advisory committees or similar organs responsible for carrying out this assignment. The proportion of reports assessed in the centre is an indication of the level of commitment to processing the safety data and ensuring its quality, especially when committing reports to the WHO database. Low values might suggest a lack of the necessary expertise to carry out causality assessment and a weak pharmacovigilance system. In some centres with large databases, causality analysis is carried out subsequent to statistical analysis of a large number of submitted reports. In these instances too, the indicator will have a low value.

Sources and methods of data collection and indicator calculation

The data for calculating this indicator should be obtained from the pharmacovigilance centre records. This should include the number of reports subjected

to causality assessment in the year under consideration and the total number of reports received in the same period. The indicator value can be calculated as follows:

$$\frac{\text{Number of reports subjected to causality assessment in the year}}{\text{Total number of reports received in the same period}} \times 100$$

Limitations

A limitation of this indicator is that it does not express the quality of causality assessment.

CP5

Percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous calendar year

Subset indicator: CP5a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database.

Definition

This indicator refers to the proportion of total reports received yearly at the pharmacovigilance centre that have all the relevant fields for causality assessment satisfactorily filled in (fields necessary for causality assessment are defined in reference *12*). Then, the subset indicator CP5a refers to those reports (satisfactorily filled in and received at the pharmacovigilance centre) that are committed to the WHO database managed by UMC.

Description and uses

The indicator value reflects the quality of reports received by the centre. It is an indication of the understanding by the health professionals of the elements in the ADR forms and the willingness and care taken to fill in the forms before submitting them to the centre. Low values of this indicator suggest a high level of poor quality reports.

The value of the subset indicator reflects the commitment of the centre to sending reports to the WHO database, which is a requirement for national pharmacovigilance centres that are full members of the WHO Programme for International Drug Monitoring.

Sources and methods of data collection and indicator calculation

The data required to calculate this indicator value should be available at the pharmacovigilance centre. Its calculation will entail a study of all the reports in the pharmacovigilance centre database to evaluate the completion of the various fields in the ADR form. For the subset indicator, it is necessary to

check whether the completed reports were sent to the WHO database. Where the pharmacovigilance centre database is large, systematic random sampling of the reports should be used to obtain an adequate number for evaluation.

The value is obtained as follows:

$$\frac{\text{[Number of reports filled satisfactorily during the year]}}{\text{[Total number of reports received during the same period]}} \times 100$$

The value of the subset indicator CP5a is obtained as follows:

$$\frac{\text{[Number of reports filled in satisfactorily } \textbf{and} \text{ committed to the WHO database during the year]}}{\text{[Total number of reports received during the same period]}} \times 100$$

Limitations

One limitation is the time and effort required to initiate the process of developing this indicator in a given setting. Once established and incorporated into the routine of the centre, the process becomes less cumbersome.

CP6

Percentage of reports of therapeutic ineffectiveness received in the previous year

Definition

This indicator identifies failed treatments owing to lack of effectiveness of medicines used in the health-care system.

Description and uses

The total number of reports received in the pharmacovigilance centre from the setting is documented. The occurrences of failed treatment in the health setting attributable to medicines suggest the existence of pharmaceutical or therapeutic issues that should be addressed. It is a useful measure that allows broad estimates of the problem of therapeutic failure and also helps measure trends in the safety of medicines.

Sources and methods of data collection and indicator calculation

The data are obtainable from the pharmacovigilance centre database and the total number of treatment failures for a given year should be documented. This is expressed as a proportion (percentage) of total reports in the database.

The indicator is calculated from the results obtained from the survey and analysed as follows:

$$\frac{\text{Number of reports of therapeutic ineffectiveness received in the year}}{\text{Total number of reports received in the same year}} \times 100$$

Limitations

The main limitation of this indicator is that it does not really capture the magnitude and the type of the problem in the setting since therapeutic ineffectiveness can be related to various factors, such as the quality of medicines, emergence of drug resistance, interactions, irrational use, or lack of pharmacological efficacy. The information obtained may also overlook issues such as the quality of reporting.

However, it is a useful measure for following the trends.

CP7

Percentage of reports on medication errors reported in the previous year

Definition

This indicator identifies failure in treatment processes that resulted in harm to patients.

Description and uses

The total number of medication errors reported to the pharmacovigilance centre from the setting is documented. The occurrence of these errors suggests the existence of fundamental systemic issues which should be addressed to ensure patient safety. The reports should be put into context, since in the early stages of operation of a pharmacovigilance centre, increasing awareness and positive disclosure patterns will mean that the reporting rates will increase. However, a study of the pattern and profile over time will be useful in identifying problems relating to medication errors that require attention.

Sources and methods of data collection and indicator calculation

The data for this indicator are obtainable from the pharmacovigilance centre database and the total number of preventable ADRs for a given year should be documented. It may be necessary to carry out an in-depth review of reports in the database to identify missed medication errors reported solely as ADRs. Absolute numbers should be documented and the trend noted over time. This value may need to be expressed as a proportion of total reports (ADRs + all other reports), especially where there is a unified reporting system.

Limitations

The main limitation of this indicator is that it does not really capture the magnitude of the medication errors in the setting since this is influenced by many other factors. However, it is a useful measure in following the trends in reporting medication errors and the factors that impact on this activity.

CP8

Percentage of registered pharmaceutical companies having a functional pharmacovigilance system

Definition

This indicator states the proportion of registered pharmaceutical companies that have a functional pharmacovigilance system.

Description and uses

The functional pharmacovigilance setting describes the provision of a standard accommodation, the engagement of a qualified person for pharmacovigilance (QPPV), an effective reporting system, development and submission of periodic safety update reports (PSURs) to appropriate authorities, and other relevant pharmacovigilance activities. It identifies the pharmaceutical outfit as a key stakeholder of pharmacovigilance. The indicator provides information on the proportion of industries in the setting that contribute towards ensuring the safety of medicines. Therefore, low values of this indicator suggest a less than acceptable level of involvement of the pharmaceutical companies in pharmacovigilance activities.

Sources and methods of data collection and indicator calculation

The relevant information can be obtained from both the pharmaceutical companies and the pharmacovigilance centre. This will include the availability of accommodation, appointed QPPV, reports to the pharmacovigilance centre and PSURs.

The indicator value can be obtained as follows:

$$\frac{\text{Number of pharmaceutical companies with a functional pharmacovigilance system}}{\text{Total number of registered pharmaceutical companies in the setting}} \times 100$$

Limitations

The main limitation of the indicator comes from the challenge in assessing the functionality of the pharmacovigilance system of the pharmaceutical companies. The extent of pharmacovigilance activity in the industries would thus need to be considered as appropriate or not ("functional or not") by the pharmacovigilance centre. This indicator requires the pharmacovigilance centre to have a clear and systematic assessment scheme for evaluating the pharmacovigilance systems of pharmaceutical companies and to use it consistently.

CP9

Number of active surveillance activities initiated, ongoing or completed in the past five calendar years

Definition

This indicator refers to the number of active surveillance efforts that are ongoing or that were conducted in the setting in the past five years.

Description and uses

The indicator measures the number of active surveillance efforts (e.g. phase 4 clinical trials, cohort event monitoring (CEM), targeted spontaneous reporting (TSR) *(13)*, pregnancy exposure registry or other epidemiological studies) that are or were implemented in the setting. Such active surveillance efforts may be critical when introducing new products for the treatment of large populations, to characterize specific adverse reactions or to focus on specific populations or problems. The value of this indicator reflects the dynamism of pharmacovigilance and regulatory activities in a setting as well as the awareness of the pharmacovigilance centre of such efforts.

Sources and methods of data collection and indicator calculation

The main sources of the data are the pharmacovigilance centre, the NRA, the public health programmes and the manufacturing industries.

Limitations

The main limitation of this indicator is that it does not provide any information about the quality of such studies. Also, the pharmacovigilance centre may not be aware of all studies conducted in the setting.

6.3 Core outcome or impact indicators

CO1

Number of signals detected in the past five years by the pharmacovigilance centre

Definition

This indicator refers to the number of instances where a signal (see Box 1 for definition), which has been identified from the national database, has been communicated outside the setting during the preceding five years.

Box 1. Definition of signal

A signal is defined as reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented. 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. In this document, signal refers to a previously unreported ADR, problems of use and poor quality medicines.

Description and uses

This indicator contributes to measuring the ability of the pharmacovigilance system to ensure the safety of medicines. This ability of the pharmacovigilance system to detect signals underscores its relevance in ensuring the safe use of medicines.

The inferences that can be drawn from this indicator include the status and stature of the database, the expertise of the pharmacovigilance staff, the dynamics of the pharmaceutical system and reporting of ADRs due to the medicines, their quality, and their use.

Sources and methods of data collection and indicator calculation

The source of information is the pharmacovigilance centre where the necessary documentation and details should be available. The indicator should be stated as the absolute values of the number of signals detected in the preceding five years.

Limitations

The limitation of this indicator is that it does not reflect the subtleties that exist in the detection of signals and the fact that causality is not implied. It provides no information about the time lag in the pharmacovigilance system before issuing a signal based on the ADR information that has been collected. The quality of the subsequent communication to the target audience (health-care professionals and/or the public) is not captured, neither is the answer to the question of whether, and if so, how the health-care providers use the information.

CO2

Number of regulatory actions taken in the preceding year consequent to national pharmacovigilance activities

Subset indicators:

CO2a: product label changes (variation)

CO2b: safety warnings on medicines

CO2b(i): to health professionals

CO2c(ii): to the general public

CO2c: drug withdrawals

CO2d: other restrictions on the use of medicines

Definition

This indicator refers to the number of regulatory actions taken in the preceding year.

Description and uses

This indicator is a measure of the regulatory decisions, based on pharmacovigilance activities, taken to ensure safety in the use of medicines in that setting. It also measures the functionality of the pharmacovigilance centre and the interface of the activities of the pharmacovigilance centre with those of the regulatory agency.

The issuance of advice and taking of appropriate actions by the regulatory authorities is a major output of the pharmacovigilance system that has enormous impact on safe use of medicines. Absence of these measures suggests non-functional or dysfunctional pharmacovigilance or regulatory systems and a failure to monitor medicines for safety.

Sources and methods of data collection and indicator calculation

The information on this indicator can be sourced from the regulatory agency records. The number and characterization of the regulatory actions are documented. Regulatory measures taken solely on the basis of information or data from other countries should not be counted.

Limitations

The limitation of this indicator is the inability to deduce its appropriateness for public health in the short term. It should also be noted that regulatory actions may be affected by factors other than the strict scientific evidence, for example, by pressure from political, media, industrial or consumer groups.

CO3

Number of medicine-related hospital admissions per 1000 admissions

Definition

This indicator refers to the number of people admitted to hospital as a result of events associated with medicines and their use.

Description and uses

This indicator is a measure of injury to health resulting from medicines – ADRs, medication errors, misuse or abuse of medicines, counterfeit/substandard medicines, and poisonings. To a large extent, it measures the effectiveness of provisions put in place to safeguard health through safe medicines and their safe use.

A high value of this indicator suggests a lack of effective mechanisms to ensure the safety and the safe use of medicines. The trend in this indicator may be used to monitor the impact of any interventions put in place to ensure patient safety. It is also a measure of the burden of medicine-related admissions to hospital and should serve to identify problems that need to be addressed.

Sources and methods of data collection and indicator calculation

The data required to calculate this indicator should be obtained from hospital records and should include:

- the number of people admitted as a result of a medicine-related illness during the study period;
- the total number of people admitted to the same hospital during the same period.

The indicator value is calculated as follows:

$$\frac{\text{Number of people admitted owing to a medicine-related illness}}{\text{Total number of people admitted to the same hospital or setting}} \times 1000$$

It is suggested to use a standard and peer-reviewed study protocol over time, such as the one proposed by Pirmohamed et al. *(14)*, to improve the quality of the measures, and to ensure reliable trend analyses.

Limitations

The limitation of this indicator is the difficulty in establishing with certainty the causal link between a medicine and an ADR. Furthermore, except in a case of poisoning, a medicine-related event is seldom considered as the underlying cause of a hospital admission and is thus not recorded at the time of hospital admission. It is believed that the number of cases of medicine-related illness is grossly underestimated owing to a low index of suspicion and lack

of awareness of such problems. An appreciable diagnostic expertise of health professionals is required to obtain reliable values.

CO4

Number of medicine-related deaths per 1000 people served by the hospital per year

Definition

The indicator refers to the number of medicine-related deaths in relation to the number of patients served by the hospital.

Description and uses

This indicator is a measure of total number of deaths resulting from medicines. Such deaths could include individuals who were outpatients and died as a result of the unsafe use of medicines – from ADRs, medication errors, misuse or abuse of medicines, dependence, interactions, counterfeit/substandard medicines, or poisonings. Or, the reported deaths could be of inpatients who were admitted to hospital as a result of a medicine-related event and later died, or those inpatients who developed a medicine-related event while in hospital and died.

The indicator will be a measure of the harmful effects of medicines in the community, on patients in hospital or patients who are not in hospital. It highlights the safety of medicines circulating in the health-care system, the appropriateness of their use by health-care personnel and the impact of the pharmacovigilance system and regulatory mechanisms in ensuring safe use of medicines. Such a mortality figure suggests systemic issues that need to be addressed to reduce the burden on the society and on the health-care system. Trends in this indicator are useful in monitoring interventions and in planning strategy.

Sources and methods of data collection and indicator calculation

The main sources of data for this indicator are hospital records. The relevant data to obtain are records of medicine-related hospital deaths and total number of hospital admissions during the relevant period.

The indicator value is calculated as follows:

$$\frac{\text{Number of medicine-related hospital deaths (outpatients and inpatients)}}{\text{Total number of inpatients and outpatients of the hospital during the period}} \times 1000$$

Limitations

The limitations noted for CO3 also apply to CO4: the main limitation on the use of this indicator is the difficulty in following up the deaths of outpatients and consequently the underestimation of the value. In addition, medicines, or their absence, might contribute to rather than cause fatalities.

A standard study protocol should be used over time to ensure reliable trend analyses.

Benchmarking between settings could be affected by differences in access to hospital care, and thus may not be valid in some instances.

CO5

Number of medicine-related deaths per 100 000 persons in the population

Definition

This indicator refers to the medicine-related mortality in the population.

Description and uses

The indicator measures the harmful effects of medicines using mortality as the end-point. It measures deaths that are related to poor practices along the entire chain, from the manufacture of the medicine, right up to its use. It is an aggregate measure of the harmful effects, including adverse reactions to medicines, medication errors, counterfeit/substandard medicines, medicine misuse or abuse and poisonings, and thus helps with plans for addressing these problems.

Sources and methods of data collection and indicator calculation

The main sources of the data should in theory be the civil registration services.

If civil registrations record less than 90% of deaths, which is the case in most developing countries *(15)*, data for this indicator would be obtained through a census, provided mortality has been recorded as being drug-related in the census records. In general, censuses are carried out at least once every 10 years, but mortality due to medicines is not systematically investigated and reported. Unfortunately, only a small number of questions are normally included on a census questionnaire, and the data collected are often of variable quality.

Alternatives to civil registration and to censuses would then need to be considered. Some countries use sample registration systems (longitudinal enumeration of demographic events, including cause of death via verbal autopsy, in a nationally representative sample of clusters, such as exists in China and India). Others implement systems such as sample vital registration with verbal autopsy (SAVVY, proposed by MEASURE Evaluation and the United States Census Bureau) to generate data needed to estimate mortality. A demographic surveillance system (DSS) may also provide a source of data for continuous surveillance of births and cause-specific mortality. Novel approaches use a hybrid set of consolidated methods based on demographic surveillance, sample registration, and the periodic use of sample cause-of-death modules using verbal autopsy within household surveys.

If data from household surveys are used, the standards for verbal autopsy as described by WHO should be met to ascertain and attribute causes of death *(16)*.

Limitations

The main limitation is usually the poor quality of the data. Obtaining data of suitable quality for this indicator is challenging, both in terms of resources (budget, time) and expertise.

To be able to document this indicator, the pharmacovigilance centres are encouraged to collaborate closely with relevant national authorities (health statistics), and in some instance also with other stakeholders such as universities, research agencies and public health programmes.

CO6

Average cost (US$) of treatment of medicine-related illness

Definition

This is a measure of the cost of treating medicine-related illness in a setting.

Description and uses

This indicator is an estimate of the financial burden imposed by medicine-related illness. It provides information on the impact on the health-care system of medicine-related illnesses. It also supports the evaluation of the costs of interventions and trends analyses. It provides useful information in planning for health care. High values of this indicator suggest major financial loss due to medicine-related illness.

Sources and methods of data collection and indicator calculation

This indicator can be obtained by experienced health economists, using cost-of-illness models such as those proposed by Johnson and Bootman *(17)* or Ernst and Grizzle *(18)*.

Limitations

The main limitation is the complexity of the calculations needed to obtain the required information and to develop (and/or replicate) an appropriate model. Other limitations would include the likelihood of non-recognition of medicine-related illness, resulting in low values. A standard study protocol should be used over time to ensure reliable trend analyses.

CO7

Average duration (days) of medicine-related extension of hospital stay

Definition

This indicator refers to hospital stays resulting from medicine-related illness.

Description and uses

The indicator measures the period of hospitalization as a result of noxious or inadvertent effects of medicines. Patients may be hospitalized owing to a medicine-related event and/or have their hospital stay prolonged as a result of some events related to medicines that were administered in hospital. The prolongation of hospital stay has important medical and economic consequences. The occupancy of hospital beds by patients with medicine-related illnesses deprives patients with other diseases of bed space for inpatient care. The indicator is a useful tool for health planning purposes. It is likely to provide information over time on the impact of medicine-related illness on the health-care system and also to enable evaluation of the impact of intervention measures. Within a hospital, it can also be used to evaluate the modalities of treatment. Lower indicator values might suggest better hospital care or a decreased occurrence of medicine-related illness.

Sources and methods of data collection and indicator calculation

The sources of the data are mainly hospitals in the setting and the data should be obtained in the course of a well-designed study, by appropriate sampling. All information relevant to the medicine-related hospital stay should be obtained in conjunction with the data required to document indicator CO8.

Limitations

An important limitation of this indicator is the personnel, time and cost required to carry out a survey. Another limitation is that it is impossible to be absolutely certain of a causal link between a drug and an ADR. An appreciable diagnostic expertise of health professionals is required to obtain reliable values. It is also believed that the number of cases of medicine-related illness is grossly underestimated owing to a low index of suspicion and a lack of awareness of such problems.

It is suggested that the required information be obtained from a standard and peer-reviewed study protocol to ensure the availability of the data, improve the quality of the measures, and ensure reliable trend analyses.

CO8

Average cost (US$) of medicine-related hospitalization

Definition

This indicator refers to the cost of hospitalization following a medicine-related illness.

Description and uses

This indicator is a measure of the financial burden on a hospital attributable to medicine-induced illness. This should be seen firstly as the costs of hospitalization necessitated by a medicine-related illness and secondly as costs resulting from prolongation of hospital stay following an in-hospital incident resulting in a medicine-related illness. It is an important measure of the impact of a medicine-related illness on the health-care system. The hospitalization of a patient with a medicine-related illness deprives other patients of hospital facilities. The economics of hospital stay also take into consideration the cost of personnel to provide care and may also reflect the treatment cost. The values of this indicator will be useful in monitoring the trends in hospitalization over time and the effects of intervention measures.

Sources and methods of data collection and indicator calculation

The data should be sourced from the hospital, from studies, or a survey of hospitals in regions or countries. A well-designed study should obtain detailed information on hospital stays of patients with medication-induced illness in designated facilities (e.g. *19–21*).

Limitations

The main limitation of this indicator is the cumbersome process of obtaining the relevant data regarding the engagement of personnel, and on the time and cost involved.

7. Description of indicators for public health programmes

This Manual proposes a set of nine pharmacovigilance indicators for public health programmes (PHPs).

Numerous PHPs are implemented in resource-limited settings. These are targeted at combating specific diseases and health issues. The majority of these programmes use medicines for prevention and/or treatment of diseases and represent a substantial investment in pharmaceuticals.[4] Given the high volumes of medicines used and the vulnerability of the population receiving these treatments, it is critical that the PHPs include a good pharmacovigilance strategy to monitor the safety and safe use of their medicines. A set of pharmacovigilance indicators dedicated to PHPs can help programme managers plan for, monitor and evaluate the effectiveness of pharmacovigilance within their programmes.

The nine indicators proposed here are intended for use by the PHP at the level of the setting. The first of these indicators (PH1) can be routinely reported to the PHP donor.[5] The remaining eight are not intended for routine reporting to the PHP donor as this would overburden both the PHP and the donor.

It should be stressed that, as far as possible, the PHP should plan and conduct pharmacovigilance activities in close collaboration with the national pharmacovigilance centre, to avoid duplication of efforts and to optimize the use of resources.

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[4] For example, close to 40% of the global amount of US$ 22 billion channelled through the Global Fund to Fight AIDS, Tuberculosis and Malaria are used to procure medicines and health products.

[5] Examples of PHP donors include The United States President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, the World Bank, UNITAID, and the Bill and Melinda Gates Foundation.

The nine pharmacovigilance indicators for public health programmes

PH1. Pharmacovigilance activities in place within the PHP

PH2. All main treatment guidelines and protocols in use within the PHP systematically consider pharmacovigilance

PH3. Existence of standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

PH3a: suspected medication errors;

PH3b: suspected counterfeit/substandard medicines;

PH3c: therapeutic ineffectiveness;

PH3d: suspected misuse, abuse of and/or dependence on medicines

PH4. Total number of ADR reports collected within the PHP in the previous year

PH5. Total number of ADR reports per 1000 individuals exposed to medicines in the PHP in the previous year

PH6. Total number of reports of therapeutic ineffectiveness in the previous year

PH7. Percentage of completed reports submitted to the national pharmacovigilance centre in the previous year

Subset indicator: PH7a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database

PH8. Number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the PHP in the previous year

PH9. Number of medicine-related deaths per 1000 individuals exposed to medicines in the PHP in the previous year

PH1

Pharmacovigilance activities in place within the public health programme

Definition

This indicator refers to the routine implementation of pharmacovigilance activities in the PHP.

Uses and description

The indicator measures the presence or absence of key pharmacovigilance activities in the PHP. Key activities include the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem. These activities need to be planned and implemented in collaboration with the pharmacovigilance centre(s), and this should occur for every

PHP that has a pharmaceutical component (using medicines for prevention and/or for treatment.) Each PHP with a pharmaceutical component is expected, *as a minimum*:

1. to report suspected ADRs to the pharmacovigilance centre, using or adapting the standard ADR form recommended by the pharmacovigilance centre, and
2. to have an open communication link with the pharmacovigilance centre, to analyse and react to drug-related problems.

Sources and methods of data collection and indicator calculation

The information should be obtained from representatives of the PHP and from the pharmacovigilance centre(s), and reported qualitatively as either present or absent. PHP workplans could also be assessed to investigate whether pharmacovigilance activities are considered and included within the set of medicines-related activities.

Limitations

The limitation of this indicator is that it reports the presence of pharmacovigilance activities without assessing the depth, quality and sustainability of the pharmacovigilance activities implemented.

Also, every PHP has different objectives, processes and targets; thus this indicator has to be defined for each PHP with a pharmaceutical component.

PH2

All the main treatment guidelines and protocols in use within the public health programme systematically consider pharmacovigilance

Definition

This indicator refers to the systematic consideration of pharmacovigilance in the main prevention and treatment guidelines and/or protocols in use within any PHP that has a pharmaceutical component.

Uses and description

This indicator measures the presence or absence of sections on pharmacovigilance in the main treatment guidelines.

Every PHP with a pharmaceutical component uses treatment guidelines and/or protocols to standardize and to enhance the quality of the treatment or drug-related prevention services. The consideration of pharmacovigilance within these documents is a major step towards ensuring that pharmacovigilance is considered by health workers and other staff involved in the PHP. On the other hand, its absence would suggest that pharmacovigilance is not considered to be important, nor consistently implemented, within the PHP.

Sources and methods of data collection and indicator calculation

The information should be obtained from the PHP representatives, as well as from a direct search of references made to pharmacovigilance within the main treatment guidelines and/or protocols. These main treatment guidelines and/or protocols would be identified, and then made available by the staff working in the PHP in the setting[6] (e.g. the managers, medical doctors, nurses, and pharmacists engaged in the treatment and/or in the prevention activities covered by the PHP). At a minimum, a form for reporting suspected ADRs to the pharmacovigilance centre should be included as an annex to these guidelines. The information is qualitative; the indicator is reported as yes if all the main documents in the PHP consider pharmacovigilance.

Limitations

The limitations of this indicator include the inability to determine whether pharmacovigilance is put into practice. Also, the assessment of pharmacovigilance in the main treatment guidelines and/or protocols depends on the availability of these documents. Some PHPs may not yet have such guidelines and relevant documents, or the staff working in the PHP may not yet be knowledgeable about them. The depth, quality and sustainability of pharmacovigilance are also not assessed.

Moreover, each PHP has different objectives, processes and targets; thus this indicator has to be defined for every PHP with a pharmaceutical component.

PH3

Existence of standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

PH3a: suspected medication errors;

PH3b: suspected counterfeit/substandard medicines;

PH3c: therapeutic ineffectiveness;

PH3d: suspected misuse, abuse of and/or dependence on medicines

Definition

This indicator refers to the use of a standard ADR reporting form with all the elements in the setting.

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[6] For example, for an HIV/AIDS treatment programme, the "main treatment guidelines and/or protocols" may include the key antiretroviral treatment protocols (first-, second- and eventually third-line, for adults and then for children), as well as protocols for the prevention of mother to child transmission and the post-exposure prophylaxis ones. As appropriate, the PHP management would also consider adding other main protocols such as the cotrimoxazole prophylaxis.

Uses and description

This indicator reports the presence of a data collection tool for pharmacovigilance operations. It suggests that the requisite tool for collecting critical information on a suspected case of medicine-related harm has been embedded in the PHP.

The reporting form should contain all elements normally required to enable causality assessment of the case based on clinical evidence.

The subset indicators show whether the ADR form includes the relevant sections to allow and to encourage practitioners to report on all the domains covered by pharmacovigilance as illustrated in Figure 1 (page 2).

Sources and methods of data collection and indicator calculation

The information should be obtained from the PHP and also from the pharmacovigilance centre, and reported qualitatively as either present or absent.

Limitations

The limitation of this indicator is that it reports the presence in the system of a reporting form and not how it is put to use. The functionality is therefore not assessed. There is no consensus regarding the elements required for the performance of evidence-based causality assessment.

The information covered by the four subset indicators may also be captured by information management tools other than the forms (e.g. from medical records), and the information is then sent to the pharmacovigilance centre.

PH4

Total number of ADR reports collected within the public health programme in the previous year

Definition

This indicator records the number of ADR reports that are collected within the PHP and shared with the pharmacovigilance centre.

Uses and description

This indicator measures the extent of involvement of the staff working in the PHP in reporting ADRs to the pharmacovigilance centre. It also reflects how well guidance on pharmacovigilance is implemented within the PHP.

The trend over time in the number of reports shared by each PHP with the pharmacovigilance centre would be useful for monitoring the involvement of each PHP in pharmacovigilance over the years, and the impact of specific activities to strengthen pharmacovigilance in PHPs.

Sources and methods of data collection and indicator calculation

The information should be obtained from the pharmacovigilance centre and from the PHP.

Limitations

The indicator does not consider the quality of the reporting in terms of content and time lag before sharing the information. It may also be difficult to link the source of reporting to the PHP; thus this indicator could not be specified.

The significance of the absolute number of reports is also difficult to interpret, since it would depend on the medicines in use and their volume, as well as other variables such as the profile of the disease. Thus the analysis of the trend in the number of reports for each PHP individually is more indicative.

PH5

Total number of ADR reports per 1000 individuals exposed to medicines in the public health programme in the previous year

Definition

This indicator refers to the number of reports on ADRs that were made within the population taking the medicines as part of the implementation of the PHP.

The main value of this additional indicator on ADRs is its potential use in comparing reporting trends and practices over time within a PHP and a setting, and eventually between comparable PHPs.

Uses and description

This indicator measures the extent of the effective involvement of the staff working in the PHP in collecting and reporting ADRs to the pharmacovigilance centre. It also reflects how well pharmacovigilance guidance is implemented within the PHP.

It provides information on the medicines' safety profile, including their quality and use, in the population exposed to medicines in the PHP.

The trend over time in the number of reports shared within each PHP would be useful to monitor the involvement of each PHP in pharmacovigilance over the years, and the impact of specific activities to promote pharmacovigilance, rational use of medicines and patient safety in the PHP.

Sources and methods of data collection and indicator calculation

The denominator "number of individuals exposed to medicines in the PHP" has to be obtained from the PHP.

The numerator, which is the number of ADRs, can be collected from the PHP or pharmacovigilance centre through active surveillance programmes (e.g. targeted spontaneous reporting or cohort event monitoring) or passive ones.

Limitations

The limitations noted for other indicators for PHPs also apply to this specific indicator:

- This indicator measures the number of case reports submitted that contain the four core data elements that constitute a valid report. The quality of documentation or relevance for signal identification will not be measured.
- It cannot be said with certainty whether a low number of ADR reports is due to poor pharmacovigilance practices, low capacities, or to safe medicines/appropriatese of medicines.
- It may also be difficult to link the source of reports to the PHP in case of spontaneous reports; thus this indicator may not be accurately measured.
- The absolute number is also difficult to interpret, as it depends on the medicines in use and their volume, as well as other variables such as the profile of the disease. Thus the analysis of the trend in the number of reports for each PHP is more indicative. To a lesser extent, comparison of number of ADRs for a PHP in different settings would also provide useful information, which would need to be cautiously interpreted by taking into account variables such as the characteristics of the population engaged in the PHP.
- Comparing the value of this indicator between different PHPs needs to be done with caution, as many variables would affect the validity of the conclusion that could be drawn from such an analysis. Nevertheless, such comparisons can contribute to an overview of the patient safety profile between different PHPs provided the limitations are identified and acknowledged.

PH6

Total number of reports on therapeutic ineffectiveness in the previous year

Definition

This indicator identifies failed treatment owing to lack of effectiveness of medicines used in the PHP.

Description and uses

The total number of reports received in the pharmacovigilance centre from the PHP is documented. The occurrences of treatment failure attributable to medicines in use in the PHP suggest the existence of pharmaceutical or therapeutic issues that should be addressed.

Sources and methods of data collection and indicator calculation

The data are obtainable from the PHP or the pharmacovigilance centre database and the total number of reports on therapeutic ineffectiveness for a given year should be documented. This is expressed as a proportion (percentage) of the total reports in the database.

The indicator is calculated from the results obtained from the survey and analysed as follows:

$$\frac{\text{[Number of reports of therapeutic ineffectiveness received in the year from a PHP]}}{\text{[Total number of reports received in the same year from the same PHP]}} \times 100$$

Limitations

The main limitation of this indicator is that it does not really capture the magnitude and the type of the problem in the setting since therapeutic ineffectiveness can be related to several factors such as the quality of medicines, emergence of drug resistance, interactions, irrational use, or to lack of pharmacological efficacy. The information obtained may also overlook issues such as the quality of reporting. The capacity to link the origin of the ADR report on therapeutic ineffectiveness to the PHP may also be lacking in some settings.

However, it is a useful measure in following the trends within a PHP.

PH7

Percentage of completed reports submitted to the national pharmacovigilance centre in the previous year

Subset indicator: PH7a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database.

Definition

This indicator refers to the proportion of total reports received yearly from the PHP at the pharmacovigilance centre, with all the fields relevant for causality assessment satisfactorily filled in.[7] The subset indicator PH7a refers to those reports (satisfactorily completed and received at the pharmacovigilance centre), which are uploaded to the WHO database.

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[7] Fields necessary for causality assessment are defined at: http://who-umc.org/graphics/26534.pdf

Description and uses

The indicator value reflects the quality of reports received by the centre. It is an indication of the understanding by health professionals of the elements in the ADR forms, and of the willingness and care taken to fill in the forms properly before submitting them to the pharmacovigilance centre. Low values of this indicator suggest a high number of poor quality reports.

The value of the subset indicator reflects the commitment of the centre to sending reports to the WHO database, which is a requirement for national pharmacovigilance centres that are full members of the WHO Pharmacovigilance Programme.

Sources and methods of data collection and indicator calculation

The data required to calculate this indicator value should be available at the pharmacovigilance centre. Data collection will entail a study of all the reports in the pharmacovigilance centre database to evaluate the completion of the various fields on the ADR form. For the subset indicator, it is necessary to check whether the completed reports were sent to the WHO database. Where the pharmacovigilance centre database is large, systematic random sampling of the reports should be used to obtain an adequate number of reports for evaluation.

The value is obtained as follows:

$$\frac{\text{[Number of reports from the PHP filled in satisfactorily during the year]}}{\text{[Total number of reports received from the PHP during the same period]}} \times 100$$

The value of the subset indicator PH7a is obtained as follows:

$$\frac{\text{[Number of reports from the PHP filled in satisfactorily } \textbf{and} \text{ committed to WHO database during the year]}}{\text{[Total number of reports from the PHP received during the same period]}} \times 100$$

Limitations

An important limitation is the time and effort required to initiate the process of developing this indicator in a given setting. Once established and incorporated into the routine of the centre, the process becomes less cumbersome.

A limitation caused by the inability to systematically identify the source of reports (as coming from the PHP) may apply in some settings.

PH8

Number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the public health programme in the previous year

Definition

This indicator refers to the number of patients admitted to hospital as a result of events associated with the use of PHP medicines within the population exposed to the medicines in the PHP.

Description and uses

This indicator is a measure of injury to health resulting from the medicine and its unsafe use – ADRs, medication errors, misuse or abuse of medicines, dependence, interactions, counterfeit/substandard medicines, and poisonings. To a large extent, it measures the effectiveness of provisions put in place to safeguard health through the safe use of medicines.

A high value of this indicator suggests a lack of effective mechanisms to ensure the safety and the safe use of medicines in the PHP. The trend in this indicator may be used to monitor the impact of any interventions intended to ensure patient safety. It is also a measure of the burden of medicine-related admissions and should serve to identify problems that should be considered.

Sources and methods of data collection and indicator calculation

The data for this indicator should be obtained from the PHP records of active follow-up of a population exposed to medicines within the programme (e.g. for targeted spontaneous reporting (TSR) or cohort event monitoring (CEM)).

Alternatively, the hospital records may be a source of information for the numerator (A below). This would be the case if the link with the PHP ("attributability" of the medicines in use by the PHP as the reason for hospital admission) can be defined in the hospital records.

The information required is:

A. number of patients admitted to hospital with a medicine-related illness attributable to a preventive or healing regimen of the PHP, taken during the previous year

B. total number of individuals exposed to medicines in the PHP

The indicator value is calculated as follows: $\frac{A}{B} \times 1000$

Limitations

As for indicator CO3, the main limitation is that it is impossible to be absolutely certain of a causal link between a medicine and an ADR. An appreciable diagnostic expertise of health professionals is required to obtain reliable values. It is also believed that the number of cases of medicine-related illness is grossly underestimated owing to a low index of suspicion and a lack of awareness of such problems.

The difficulty of linking the medicine-related ADR to the specific medicine taken in the PHP is another limitation to be considered.

It is suggested that the required information is obtained from a standardized and peer-reviewed study protocol for TSR or for CEM, to ensure the availability of the data, to improve the quality of the measures, and to ensure reliable trend analyses.

PH9

Number of medicine-related deaths per 1000 individuals exposed to medicines in the public health programme in the previous year

Definition

The indicator refers to the number of PHP medicine-related deaths in the previous year among individuals exposed to medicines within the PHP.

Description and uses

This indicator is a measure of total number of deaths resulting from PHP medicine-related illness, attributable to any of the medicines provided by the PHP. In other words, the indicator will provide a measure of deaths due to PHP medicines and their unsafe use – ADRs, medication errors, misuse/abuse of medicines, dependence, interactions, counterfeit/substandard medicines, or poisonings. It highlights the safety of medicines circulating in the PHP, the appropriateness of their use by health-care personnel and the impact of the pharmacovigilance system and regulatory mechanisms in ensuring safe use of medicines in the PHP. The mortality figure suggests systemic issues that need to be addressed to reduce the burden on society and on the health-care system. Trends in this indicator are useful in monitoring interventions and in planning strategy.

Sources and methods of data collection and indicator calculation

The main sources of data should be the PHP records. The relevant data that should be obtained are records of medicine-related deaths associated with medicines taken as part of the PHP, and total number of individuals taking those medicines in the PHP.

Alternatively, as for PH8, the hospital records may be a source of information.

The indicator value is calculated as follows:

$$\frac{\text{Number of PHP medicine-related deaths during the year}}{\text{Total number of individuals exposed to medicines in the PHP during the year}} \times 1000$$

Limitations

The limitations noted for PH8 also apply to PH9. In addition, deaths are not always recorded or reported, leading to underestimation of the indicator value.

A standard study protocol, rooted within a TSR or a CEM effort, should be used over time to ensure reliable trend analyses.

References

1. World Health Organization and Global Fund. Minimum requirements for a functional pharmacovigilance system. Geneva: World Health Organization; 2010 (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2_en.pdf, accessed 7 April 2014).
2. Venulet J, Helling-Borda M. WHO's international drug monitoring – the formative years, 1968–1975 preparatory, pilot and early operational phases. Drug Saf. 2010;33(7):e1–e23.
3. Edwards IR, Aronson JK. Adverse drug reactions: definitions, classification, diagnosis, management, surveillance. Lancet. 2000;356:1255–60.
4. Lindquist M. The need for definitions in pharmacovigilance. Drug Saf. 2007;30(10):825–30.
5. Indicators for quality use of medicines in Australian hospitals. NSW Darlinghurst: New South Wales Therapeutic Advisory Group; 2007.
6. The importance of pharmacovigilance. Safety monitoring of medicinal products. Geneva: World Health Organization; 2002.
7. WHO operational package for assessing, monitoring and evaluating country pharmaceutical situations. Guide for coordinators and data collectors. Geneva: World Health Organization; 2007.
8. Report of the Thirty-first Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, 20–23 October 2008. WHO Pharmaceuticals Newsletter. 2008;4 (http://www.who.int/medicines/publications/newsletter/2008news4.pdf, accessed 7 April 2015).
9. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries. A questionnaire-based analysis. Drug Saf. 2010;33(8):689–703.
10. Thirty-second Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. Geneva: World Health Organization (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/nat_cent_meeting/en/index.html, accessed 7 April 2015).

11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH harmonized tripartite guideline. Clinical safety data management: definitions and standards for expedited reporting. E2A. Geneva: ICH; 1994.

12. Individual Case Safety Reports and VigiBase – the vital importance of quality. Uppsala: Uppsala Monitoring Centre; 2012 (http://who-umc.org/graphics/26534.pdf, accessed 7 April 2015).

13. Pal S, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75–81. doi: 10.1007/s40264-012-0014-6.

14. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as a cause of admission to hospital: a prospective analysis. BMJ. 2004;329(7456):15–9.

15. Health Metrics Network. Assessing the national health information system: an assessment tool. Version 4.00. Geneva: World Health Organization; 2008 (http://www.who.int/healthmetrics/tools/Version_4.00_Assessment_Tool3.pdf, accessed 7 April 2015).

16. Health statistics and information systems. The 2012 WHO verbal autopsy instrument. Geneva: World Health Organization, 2012 (http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/, accessed 7 April 2015).

17. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. Arch Int Med. 1995;155:1949–56.

18. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc. 2001;41:192–9.

19. Pattanaik S, Dhamija P, Malhotra S, Sharma N, Pandhi P. Evaluation of cost of treatment of drug-related events in a tertiary care public sector hospital in Northern India: a prospective study. Br J Clin Pharmacol.2008;67(3):363–9.

20. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277:301–6.

21. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital – their severity and cost involved. Pharmacoepidemiol Drug Saf. 2003;12:687–92.

Further reading

How to investigate drug use in health facilities. Geneva: World Health Organization; 1993.

How to investigate the use of medicines by consumers. Geneva: World Health Organization; 2004.

Indicators for monitoring drug policy. Geneva: World Health Organization; 1999.

The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: World Health Organization; 2002.

Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Geneva: WHO and the Uppsala Monitoring Centre (UMC), WHO Collaborating Centre for International Drug Monitoring; 2000 (http://apps.who.int/medicinedocs/en/d/Jh2934e/, accessed 1 February 2015).

Pharmacovigilance: ensuring the safe use of medicines. WHO Policy Perspectives on Medicines 9, 2004 (http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf, accessed 1 February 2015).

Using indicators to measure country pharmaceutical situations. Fact book on WHO Level I and Level II monitoring indicators. Geneva: World Health Organization; 2006.

Meyboom, RH, Lindquist M, Flygare AK, Biriell C, Edwards IR. The value of reporting therapeutic ineffectiveness as an adverse drug reaction. Drug Saf. 2000;23(2):95–9. This article and 11 other core articles by Edwards R, Lindquist M, Meyboom R, Olsson S, et al., previously published in Drug Safety, were reprinted in a collection entitled Pharmacovigilance in focus – the theory and practice of pharmacovigilance, and are now freely accessible in the Publications section of the Uppsala Monitoring Centre website (http://who-umc.org/, accessed 1 February 2015).

Indicator-based pharmacovigilance assessment tool: manual for conducting assessments in developing countries. Submitted to the US Agency for International Development by the SPS Program. Arlington (VA): Management Sciences for Health. Strengthening Pharmaceutical Systems (SPS) Program; 2009.

Nilima A Kshirsagar, Sten Olsson, Robin E Ferner. Consideration of the desirable features and possible forms of practical indicators of the performance of pharmacovigilance centres. International Journal of Risk and Safety in Medicine, 2010;22:59–66.

Annexes

Annex 1

Minimum requirements for a functional pharmacovigilance system

The functions of a national pharmacovigilance system include the following:

1. To promote pharmacovigilance in the country, notably, to collect and manage adverse drug reaction (ADR) reports, reports of medication errors and suspected counterfeit/substandard drugs.
2. To collaborate and harmonize with existing ADR report collection activities within the country (e.g. national disease control programmes, ministry of health) as well as international studies that are monitoring ADRs in defined patients or populations (cohorts).
3. To identify signals, i.e. unknown or poorly characterized adverse events in relation to a medicine or a combination of medicines and/or its use.
4. To undertake assessment of risk and options for risk management.
5. To identify quality problems in medicines resulting in ADRs; and more generally, to support the identification of medicine quality issues.
6. To provide effective communication on aspects related to medicine safety, including dispelling unfounded rumours of toxicity attributed to medicines and/or vaccines.
7. To apply information resulting 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.

Minimum requirements for a functional national pharmacovigilance system

The following are the minimum requirements that WHO and partners agree should be met in any national pharmacovigilance system.

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. a national spontaneous reporting system with a national individual case safety report (ICSR) form, i.e. an 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 communication strategy for routine communication and communication during crises.

ANNEX 2
Background information

The background information define and describe the milieu where the pharmacovigilance activities are taking place and other factors likely to impact on pharmacovigilance. The information will cover demographics, economics, the health-care system and pharmaceutical scenario.

They provide the denominator for calculating most of the indicator values. They include the following:

BG1. Total population of the setting (country, region or facility) .....

BG2. Sex and age structure of the population

a. male:female .....

b. life expectancy .....

c. dependency ratio .....

BG3. Total number of drug manufacturing units in the country .....

BG4. Total number of pharmaceutical establishments in the country .....

BG5. Total number of pharmacies and drug outlets in the country .....

a. public .....

b. private .....

BG6. Total number of registered drugs (including all brand names)

a. prescription only .....

b. pharmacy sale only .....

c. general sale .....

BG7. Total number of medicines in the national list of essential medicines .....

BG8. What proportion of drugs are sold or obtained in the informal sector .....

BG9. Percentage of medicines that are counterfeit/substandard in the pharmaceutical market .....

BG10. Total number of hospitals and clinics .....

a. public .....

b. private .....

BG11. Total no. of health professionals in each category .....

a. doctors .....

b. dentists .....

c. pharmacists .....

d. nurses .....

e. others .....

Annex 3
Assessment checklist

Introductory statement

This assessment checklist is proposed as a ready-to-use tool for collecting and reporting the value of each indicator. Assessors should document the source of data used to identify the indicator value.

The checklist also includes a column in which to record the next steps envisaged to improve the situation, from the perspective of various staff members interviewed during the assessment. The assessor is encouraged to report such perspectives to the extent possible; ideally, the institution and/or the staff who expressed the idea should be referenced, if this does not constitute a breach of confidentiality.

As for other WHO manuals,[8] it should be stressed that the assessment should be based as far as possible on documented evidence; assessments should not be based on impressions, feelings or any subjective considerations. The assessor should collect objective evidence of his/her observation, e.g. published laws or regulations should be collected and a reference to internal procedures and standard operating procedures or instructions should be quoted.

> The evidence will be collected by different means such as: interviewing personnel, reading documents, reviewing manuals, studying records, reading reports, scanning files, analysing data, observing activities, examining conditions (include site visits).

An assessment is not a desk verification: the assessor should not limit his/her activities to checking the presence or the absence of a document or a law. She or he should, as far as possible, pursue the evidence of the implementation of the procedures, guidance or laws.

> For example, a law might have been published but no regulation has subsequently been adopted or the regulation has not been explained to other stakeholders through appropriate guidance. As regards the administrative procedures, the questioning methodology is the same; a procedure

[8] e.g A WHO manual for assessment of the national regulatory system for vaccines: draft_manual_NRA_assessment_part_3_revOct2011.01

might have been established but not implemented. In such cases, the assessors should take samples of the records to identify the level of implementation of the procedure.

An assessment is not an inspection: it is a method to improve a pharmacovigilance system, and it could be performed within the organization by internal personnel, by an external expert, or by a third party such as WHO. It should not be understood as a means to enforce specific procedures or practices or to coerce people to act in a specific manner. Assessment provides general recommendations that need to be discussed to help the Member States to enforce them.

This assessment checklist has three parts: the first part refers to core indicators; the second to complementary indicators and the third part refers to pharmacovigilance indicators for public health programmes.

PART 1: CORE INDICATORS

CORE STRUCTURAL INDICATORS

	Assessment questions	Data sources used	Answer (yes/no, or value)	Optional: proposed next steps?
CST1	Is there a pharmacovigilance centre, department or unit with a standard accommodation?			
CST2	Is there a statutory provision (national policy, legislation) for pharmacovigilance?			
CST3	Is there a drug regulatory authority or agency?			
CST4	Is there any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre?			
CST5	Does the pharmacovigilance centre have human resources to carry out its functions properly?			
CST6	Is there a standard ADR reporting form in the setting?			
	CST6a: Are there relevant fields in the standard ADR form to report suspected medication errors?			
	CST6b: Are there relevant fields in the standard ADR form to report suspected counterfeit/ substandard medicines?			
	CST6c: Are there relevant fields in the standard ADR form to report therapeutic ineffectiveness?			
	CST6d: Are there relevant fields in the standard ADR form to report suspected misuse, abuse and/or dependence on medicines?			
	CST6e: Is there a standard ADR reporting form for the general public?			
CST7	Is there a process in place for collection, recording and analysis of ADR reports?			
CST8	Is pharmacovigilance incorporated into the national curriculum of the various health care professions?			

Core structural indicators *(continued)*				
	Assessment questions	**Data sources used**	**Answer (yes/no, or value)**	**Optional: proposed next steps?**
CST8	CST8a: Is pharmacovigilance incorporated into the national curriculum of medical doctors?			
	CST8b: Is pharmacovigilance incorporated into the national curriculum of dentists?			
	CST8c: Is pharmacovigilance incorporated into the national curriculum of pharmacists?			
	CST8d: Is pharmacovigilance incorporated into the national curriculum of nurses or midwives?			
	CST8e: Is pharmacovigilance incorporated into the national curriculum of others – to be specified?		(yes/no, **and** specify "others")	
CST9	Is there a newsletter, information bulletin or website (a tool for pharmacovigilance information dissemination?)			
CST10	Is there a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety?			
CORE PROCESS INDICATORS				
CP1	What is the total number of ADR reports received in the previous year?			
	CP1a: What is the total number of ADR reports received in the previous year per 100 000 people in the population?			
CP2	How many reports are (current total number) in the national/regional/local database?			
CP3	What is the percentage of total annual reports acknowledged/issued feedback?			
CP4	What is the percentage of total reports subjected to causality assessment in the past year?			

	Assessment questions	Data sources used	Answer (yes/no, or value)	Optional: proposed next steps?
CP5	What is the percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous year?			
	CP5a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, what percentage were committed to the WHO database?			
CP6	What is the percentage of reports of therapeutic ineffectiveness received in the previous year?			
CP7	What is the percentage of reports on medication errors reported in the previous year?			
CP8	What percentage of registered pharmaceutical companies have a functional pharmacovigilance system?			
CP9	How many active surveillance activities are or were initiated, ongoing or completed in the past 5 years?			
CORE OUTCOME/IMPACT INDICATORS				
CO1	How many signals were generated in the past 5 years by the pharmacovigilance centre?			
CO2	How many regulatory actions were taken in the preceding year consequent on national pharmacovigilance activities?			
	CO2a: how many product label changes (variation)?			
	CO2b: how many safety warnings on medicines to: CO2bi, health professionals CO2bii, the general public?			
	CO2c: how many withdrawals of medicines?			
	CO2d: how many other restrictions on use of medicines?			

Core outcome/impact indicators *(continued)*				
	Assessment questions	**Data sources used**	**Answer (yes/no, or value)**	**Optional: proposed next steps?**
CO3	What is the number of medicine-related hospital admissions per 1000 admissions?			
CO4	What is the number of medicine-related deaths per 1000 persons served by the hospital per year?			
CO5	What is the number of medicine-related deaths per 100 000 persons in the population?			
CO6	What is the average cost (US$) of treatment of medicine-related illness?			
CO7	What is the average duration (days) of medicine-related extension of hospital stay?			
CO8	What is the average cost (US$) of medicine-related hospitalization?			
PART 2: COMPLEMENTARY INDICATORS				
COMPLEMENTARY STRUCTURAL INDICATORS				
ST1	Is there a dedicated computer for pharmacovigilance activities?			
ST2	Is there a source for data on consumption and prescription of medicines?			
ST3	Are there functioning and accessible communication facilities in the pharmacovigilance centre?			
ST4	Is there a library or any other reference source for drug safety information?			
ST5	Is there a computerized case report management system?			
ST6	Is there a programme (including a laboratory) for monitoring the quality of pharmaceutical products?			
	ST6a: Is the programme (including a laboratory) for monitoring the quality of pharmaceutical products, collaborating with the pharmacovigilance programme?		Not applicable or yes or no	

	Assessment questions	Data sources used	Answer (yes/no, or value)	Optional: proposed next steps?
ST7	Is there an essential medicines list in use?			
ST8	Are pharmacovigilance data considered when developing the main standard treatment guidelines?			
ST9	Does the pharmacovigilance centre organize training courses? ST9a: for health professionals? ST9b: for the general public?			
ST10	Are web-based pharmacovigilance training tools available? ST10a: for health professionals? ST10b: for the general public?			
ST11	Are there requirements mandating market authorization holders to submit periodic safety update reports?			
COMPLEMENTARY PROCESS INDICATORS				
P1	Last year, what was the percentage of health-care facilities that had a functional pharmacovigilance unit (i.e. submits ≥ 10 reports annually to the pharmacovigilance centre)?			
P2	What was the percentage of total reports sent in the previous year by the different stakeholders:			
	P2a: percentage of the total reports sent by medical doctors			
	P2b: percentage of the total reports sent by dentists			
	P2c: percentage of the total reports sent by pharmacists			
	P2d: percentage of the total reports sent by nurses or midwives			
	P2e: percentage of the total reports sent by members of the general public			
	P2f: percentage of the total reports sent by manufacturers			

Complementary process indicators *(continued)*				
	Assessment questions	**Data sources used**	**Answer (yes/no, or value)**	**Optional: proposed next steps?**
P3	What is the total number of reports received per million population per year?			
P4	What is the averagenumber of reports per total number of health-care providers per year?			
	P4a: number of reports per total number of medical doctors			
	P4b: Average number of the total of reports sent by dentists			
	P4c: Average number of the total of reports sent by pharmacists			
	P4d: Average number of the total of reports sent by nurses or midwives			
P5	What is the percentage of health-care providers aware of and knowledgeable about ADRs per health facility?			
P6	What is the percentage of patients leaving a health facility aware of ADRs in general?			
P7	How many face to face training sessions were conducted on pharmacovigilance in the previous year? P7a: number of face to face pharmacovigilance training sessions for health professionals P7b: number of face to face pharmacovigilance training sessions for general public			
P8	How many individuals received face to face training in pharmacovigilance in the previous year? P8a: number of health professionals P8b: number of individuals from general public			
P9	How many national reports for a specific product per volume of sales of that product in the country (product specific) from the industry?			

	Assessment questions	Data sources used	Answer (yes/no, or value)	Optional: proposed next steps?
P10	How many registered products with a pharmacovigilance plan and/or a risk management strategy from market authorization holders exist in the country?			
	P10a: what is the percentage of registered products with a pharmacovigilance plan and/or a risk management strategy from market authorization holders in the country?			
P11	What is the percentage of market authorization holders submitting periodic safety update reports (PSURs) to the regulatory authority as stipulated in the country?			
P12	Last year, how many products were voluntarily withdrawn by market authorization holders because of safety concerns?			
	P12a: Last year, how many summaries of product characteristics (SPCs) were updated by market authorization holders because of safety concerns?			
P13	How many reports per each registered pharmaceutical industry were received by the pharmacovigilance centre in the previous year?		One number per registered pharmaceutical company	
COMPLEMENTARY OUTCOME/IMPACT INDICATORS				
O1	What is the percentage of preventable ADRs out of the total number of ADRs reported in the preceding year?			
O2	How many medicine-related congenital malformations per 100 000 births?			
O3	Number of medicines found to be possibly associated with congenital malformations in the past 5 years			
O4	Percentage of medicines that are counterfeit/substandard in the pharmaceutical market			
O5	Number of patients affected by a medication error in hospital per 1000 admissions in the previous year			

Complementary outcome/impact indicators *(continued)*				
	Assessment questions	**Data sources used**	**Answer (yes/no, or value)**	**Optional: proposed next steps?**
O6	Average work or schooldays lost due to drug-related problems			
O7	Cost savings (US$) attributed to pharmacovigilance activities			
O8	Health budget impact (annual and over time serial) attributed to pharmacovigilance activity			
O9	Average number of medicines per prescription			
O10	Percentage of prescriptions with medicines exceeding recommended dose			
O11	Percentage of prescriptions containing medicines with potential for interaction			
O12	Percentage of patients receiving information on the use of their medicines and on potential ADRs associated with those medicines			
PART 3: INDICATORS FOR PUBLIC HEALTH PROGRAMMES (PHP)				
PH1	Are pharmacovigilance activities in place within the public health programme (PHP)?			
PH2	Do all main treatment guidelines or protocols in use within the PHP systematically consider pharmacovigilance			
PH3	Is there a standard ADR reporting form in the setting?			
	PH3a: are there relevant fields in the standard ADR form to report suspected medication errors?			
	PH3b: are there relevant fields in the standard ADR form to report suspected counterfeit/substandard medicines?			
	PH3c: are there relevant fields in the standard ADR form to report therapeutic ineffectiveness?			

	Assessment questions	Data sources used	Answer (yes/no, or value)	Optional: proposed next steps?
PH3	PH3d: are there fields in the standard ADR form to report suspected misuse, abuse and/or dependence on medicines?			
PH4	What is the total number of ADR reports collected within the PHP in the previous year?			
PH5	How many ADR reports (per 1000 individuals exposed to medicines in the PHP) were reported in the previous year?			
PH6	How many reports on therapeutic ineffectiveness were made in the previous year?			
PH7	What percentage of completed reports were submitted to the national pharmacovigilance centre in the previous year?			
	PH7a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, what is the percentage of reports committed to the WHO database?			
PH8	What is the number of medicine-related hospital admissions per 1000 individuals exposed to medicines in the PHP in the previous year?			
PH9	What is the number of medicine-related deaths per 1000 individuals exposed to medicines in the PHP in the previous year?			

This publication provides a practical method for determining the pharmacovigilance (PV) indices. It has been designed to be simple and to be understood by any PV worker without formal training in monitoring and evaluation and should be regularly used in PV establishments.

The indicators proposed in this publication are based on the expected functions of PV centres. The structural, process and outcome or impact indicators described should be used as tools for quality assurance and improvement of PV establishments and services.

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