COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

CIOMS Cumulative Pharmacovigilance GLOSSARY

Version 1.1

CIOMS

Geneva 2021

CIOMS Cumulative Pharmacovigilance Glossary: Version 1.1

FOREWORD

Suggested citation

CIOMS Cumulative Pharmacovigilance Glossary, Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2021. doi: 10.56759/simv6903

Authors and reviewers

This publication was compiled by Stella Blackburn, Stephen Heaton and Panos Tsintis, all of whom have contributed to at least one CIOMS pharmacovigilance Working Group (WG) report, with assistance from Sanna Hill, Kateriina Rannula and Monika Zweygarth and with guidance from Lembit Rägo, Secretary General of CIOMS. The original inspiration came from Stephen Heaton at the time of writing the CIOMS WG IX Report, Practical Approaches to Risk Minimisation for Medicinal Products. CIOMS also thanks Priya Bahri for reviewing the draft and making useful suggestions for improvements.

Introduction

Since its inception, CIOMS has published over 10 reports on various topics in the field of pharmacovigilance, and this CIOMS Cumulative Pharmacovigilance Glossary compiles all the definitions within these reports. The current SARS-CoV-2 pandemic seems to be a particularly appropriate time to publish this glossary, given the increased interest in pharmacovigilance globally to address the safety and effectiveness of medicinal products for the prevention and treatment of COVID-19. As the science and practice of pharmacovigilance have evolved over the past decades, so too have the related definitions. New terms have been introduced, existing definitions have been modified, and some terms have disappeared from use.

In this glossary, the most recent CIOMS definition is the default one emphasised, and historical definitions have been kept for reference and because they are sometimes still seen in use. True synonyms have been grouped together and some marked differences in definitions have been noted between different jurisdictions. The terms and definitions are referenced according to the original CIOMS reports where they first appeared, and where applicable, according to the sources they were modified from. The CIOMS pharmacovigilance reports referenced are shown under Reports referenced and change history below.

Going forward, CIOMS intends to maintain this glossary as a living document on the CIOMS website, pharmacovigilance page and welcomes all feedback. Thank you for emailing recommendations to info@cioms.ch.

As new CIOMS reports are published, more terms and definitions will be added. At the time of writing, four new CIOMS pharmacovigilance reports are being prepared:

- Patient Involvement in the Development and Safe Use of Medicines (CIOMS XI);
- Benefit-Risk Balance for Medicinal Products (CIOMS XII) - this will be an update of CIOMS IV on Benefit-Risk Balance for Marketed Drugs: Evaluation of Safety Signals, originally published in 1998;
- Real-World Data and Real-World Evidence in Regulatory Decision Making (CIOMS XIII);
- Severe Cutaneous Adverse Reactions of Drugs (SCARs).

The CIOMS Cumulative Pharmacovigilance Glossary does not cover CIOMS reports on the subjects of ethics, clinical pharmacology, product development, the Medical Dictionary for Regulatory Activities (MedDRA®), or publications resulting from CIOMS Roundtable Discussions.

How to use the glossary

The example below shows the different visual styles used throughout this glossary to designate different types of information. Abbreviations are given in full in each glossary entry, except for some commonly recurring abbreviations (*e.g.* CIOMS, ICH, EU) listed underneath the example.

1. **Glossary term** including synonyms or other terms to review (CIOMS Working Group report where the current definition appears – translations if any)
   {Potential synonyms or other terms to review as suggested by the Glossary Advisory Board}

   Definition of the term.

   Source of the term and its definition. If the term and/or its definition have been modified or combined with another definition, this is stated.

   Information about how different jurisdictions handle the same term. This section may begin with, for example: "In the EU …"

   Commentary from the CIOMS Working Group that provided the term and its definition.

   {Comment from the Glossary Advisory Board}

   {Glossary Advisory Board's notes on evolving terms in red font}

Evolving definition

→ A link to the term under TERMS AND DEFINITIONS — VACCINES, if applicable.

The term as it appeared in a previous CIOMS report (CIOMS Working Group report where the term appeared – translations if any)

Definition of the term.

Source of the term and its definition. If the term and/or its definition have been modified or combined with another definition, this is stated.

Commentary from the CIOMS Working Group that provided the term and its definition.

{Comment from the Glossary Advisory Board}

Recurring abbreviations

Art	Article
CIOMS	Council for International Organizations of Medical Sciences
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (until 2015: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
EC	European Commission
EMA	European Medicines Agency
EU	European Union
GVP	Guideline on good pharmacovigilance practices (European Union)
FDA	Food and Drug Administration (United States)
Rev	Revision
U.S.	United States of America
WG	Working group (CIOMS)
WHO	World Health Organization

CIOMS Cumulative Pharmacovigilance Glossary Advisory Board

Following the publication of the CIOMS Cumulative Pharmacovigilance Glossary Version 1.0, an Advisory Board was formed, including a variety of different stakeholders, to meet periodically to review all feedback received and prepare the changes, which may include edited definitions that need to be brought in line with contemporary pharmacovigilance.

Disclaimer

The CIOMS Cumulative Pharmacovigilance Glossary includes CIOMS' recommended definitions for terms used in pharmacovigilance and is for general informational and educational purposes only. Readers are encouraged to verify the original sources for exact wording and asked to bear in mind that the CIOMS Cumulative Pharmacovigilance Glossary makes reference to many third-party publications and websites; and while CIOMS strives to provide only quality, up-to-date references, it has no control over the content found in later, third-party publication editions or website updates.

As a case in point, where definitions originated from the EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014), an effort has been made to confirm the definitions have remained unchanged in the later publication, the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)[1]. In this context, also note that Revision 3 of the EU Module XVI on Risk minimisation measures: selection of tools and effectiveness indicators and its new Addendum II on methods for effectiveness evaluation of risk minimisation measures were under public consultation until 28 April 2021.

Reports referenced and change history

Version	Content / change	Date
1.1	Added terms from the following reports of the two vaccine-related CIOMS Working Groups (WGs), i.e. the CIOMS/WHO WG on Vaccine Pharmacovigilance and the CIOMS WG on Vaccine Safety: • Definition and Application of Terms for Vaccine Pharmacovigilance (CIOMS/WHO WG on Vaccine Pharmacovigilance) 2012. The following sections were considered: Glossary and explanatory notes; 3. General definitions: 3.1 Vaccine pharmacovigilance; 3.2 Vaccination failure; 3.3 AEFI definitions. • CIOMS Guide to Active Vaccine Safety Surveillance (CIOMS Working Group on Vaccine Safety) 2017 — referred to as CIOMS WG on Vaccine Safety – AVSS in this glossary • CIOMS Guide to Vaccine Safety Communication (CIOMS Working Group on Vaccine Safety) 2018 — referred to as CIOMS WG on Vaccine Safety – VSC in this glossary. Definitions were located by searching for the words "term" and "definition"/"defined". Added terms from: Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials (CIOMS VII), 2006 Added terms from: International Reporting of Periodic Drug-Safety Update Summaries (CIOMS II), 1992	3 June 2021

(continued)

[1] Some additional revisions of the EU GVP Annex 1 (Revision 4) will apply when Regulation (EU) No 536/2014 becomes applicable, these are not yet reflected here.

Version	Content / change	Date
(Continued)		
1.0	Included terms from the following CIOMS reports: • Benefit-risk balance for marketed drugs: Evaluating safety signals (CIOMS IV), 1998; • Management of Safety Information from Clinical Trials (CIOMS VI), 2005; • Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS VIII, also available in Chinese), 2010; • Practical Approaches to Risk Minimisation for Medicinal Products (CIOMS IX), 2014; • Evidence Synthesis and Meta-Analysis for Drug Safety (CIOMS X) 2016; • Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. 2020. Note: The report of the first CIOMS Working Group on International Reporting of Adverse Drug Reactions (CIOMS I, 1987), the Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition (CIOMS III and V, 1999), and the report on Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V, 2001), did not include a formal glossary. No definitions from these reports are included here, but some have formed the basis of definitions proposed by subsequent Working Groups (*e.g.* see *Development core safety information (DCSI)*).	26 March 2021

Translations

CIOMS VI: Japanese (order)

CIOMS VII: Japanese (order)

CIOMS VIII: Chinese — also linked under each respective term heading; Japanese (order)

CIOMS XI: Japanese (order)

Geneva, Switzerland, June 2021

Dr Lembit Rägo, MD, PhD
Secretary-General, CIOMS

TERMS AND DEFINITIONS — GENERAL

A

1. **Absolute risk** (CIOMS VI)
The number of people in a group who experience an adverse effect divided by the number in that group who could experience that adverse effect.

Proposed by CIOMS Working Group VI.

→ Absolute risk (TERMS AND DEFINITIONS — VACCINES)

2. **Acceptable risk** (CIOMS VI)
We do not provide a definition for this concept.

Commentary: Although this term is often used, especially in connection with benefit-risk considerations, it has proven impossible to define (acceptable to whom and under what circumstances, for example?). Readers are advised that they should be aware of this concept but that acceptable risk may mean many different things depending on the context and from whose perspective. If sponsors or regulators wish to invoke the concept in assessing the value or use of a product during development, they should base their judgments on the particular circumstances of the clinical program. […] Attempts have been made to define and measure acceptable risk based on the concept of "utility" (*e.g.*, see Lane, D.A. and Hutchinson, T. The Notion of "Acceptable Risk": The Role of Utility in Drug Management, J. Chron. Dis., 40:621-625, 1987).

Proposed by CIOMS Working Group VI.

3. **Active surveillance** (CIOMS DILI)
A system for the collection of case safety information as a continuous pre-organized process.

Active surveillance can be: 1. Drug based: identifying adverse events in patients taking certain products; 2. identifying adverse events in certain healthcare settings where they are likely to present for treatment 3. Event based: identifying adverse events that are likely to be associated with medicinal products, *e.g.*, liver failure.

Adopted from: The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva, WHO, 2002.

→ See also Active vaccine safety surveillance (TERMS AND DEFINITIONS — VACCINES)

Active surveillance (CIOMS VIII, also available in Chinese)
An active surveillance system has been defined by the World Health Organization as the collection of case safety information as a continuous pre-organized process. The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. Geneva, World Health Organization, 2002.

Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (*e.g.*, emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (*e.g.* acute liver failure).

Adopted from: Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment. Rockville, MD, Food and Drug Administration (FDA), March 2005.

4. **Additional risk minimisation activity**, see also Routine risk minimisation activities (CIOMS IX)
An intervention intended to prevent or reduce the probability of an undesirable outcome, or reduce its severity should it occur, which is in addition to the routine risk minimization activities defined as requirements applied to all medicinal products in the regulations of a particular territory.

Proposed by CIOMS Working Group IX.

5. **Adoption** (CIOMS IX)
One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). Adoption refers to the participation rate and representativeness of both the settings in which an intervention is conducted and the intervention agents who deliver the intervention. Adoption is usually assessed by direct observation or structured interviews or surveys. Barriers to adoption should also be examined when nonparticipating settings are assessed.

Modified from:

Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), San Francisco: Wiley. 2008: 496–497.

Glasgow RE, Vogt TM, Boles SM. Evaluating the Public Health Impact of Health Promotion Interventions: The RE-AIM Framework. Am J Public Health. 1999, 89(9): 1322–1327.

6. **Adverse drug reaction (ADR)**, synonyms: Adverse reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect (CIOMS IX)
A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Adopted from: Definition EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (08 January 2014).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)}

Adverse drug reaction (ADR) (CIOMS VIII, also available in Chinese)
A noxious and unintended response to a medicinal product for which there is a reasonable possibility that the product caused the response. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase "a reasonable possibility" means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

Adopted from: ICH E2A Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Step 5 as of October 1994.

Note: From a regulatory perspective, all spontaneous reports are considered "suspected" ADRs in that they convey the suspicions of the reporters. A causality assessment by the regulatory authority may indicate whether there could be alternative explanations for the observed adverse event other than the suspect drug. It should be noted that although overdose is not included in the basic definition of an adverse drug reaction in the post-approval environment, information regarding overdose, abuse and misuse should be included as part of the risk assessment of any medicinal product.

Adverse Drug Reaction (CIOMS VII)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly when the therapeutic dose(s) may not be established: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out.

Source: ICH Guideline for Good Clinical Practice E6(R1)

In the EU Directive 2001/20/EC on Clinical trials: "Adverse Reaction: – all untoward and unintended responses to an investigational medicinal product related to any dose administered."

Commentary: As shown, the current ICH definition includes the phrase "*i.e.*, the relationship cannot be ruled out." The CIOMS Working Group believes that it is virtually impossible to rule out with any certainty the role of the drug on the basis of a single case. Therefore, we recommend elimination of that phrase and prefer the ICH E2A elaboration of "reasonable possibility" to mean that there are facts, evidence, or arguments to support a causal association with the drug.

Adverse drug reaction (ADR) (CIOMS VI)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly when the therapeutic dose(s) may not be established: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out.

Adopted from: ICH Guideline E6: Good Clinical Practice

In the EU: "Adverse Reaction" – all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Commentary: As shown, the current ICH definition includes the phrase "*i.e.*, the relationship cannot be ruled out." The CIOMS Working Group believes that it is virtually impossible to rule out with any certainty the role of the drug on the basis of a single case. Therefore, we recommend elimination of that phrase and prefer the ICH E2A elaboration of "reasonable possibility" to mean that there are facts, evidence, or arguments to support a causal association with the drug.

7. **Adverse event (AE)**, synonym: Adverse experience (CIOMS IX)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (08 January 2014).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)}

→ See also Adverse event following immunization (AEFI) (TERMS AND DEFINITIONS — VACCINES)

Adverse event (AE) (CIOMS VIII, also available in Chinese)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

Note: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adopted from: Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline, E6(R1), Current Step 4 version, dated 10 June 2006 (including Post Step 4 corrections).

Adverse event/Adverse experience (CIOMS VII)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Source: ICH Guideline for Good Clinical Practice E6(R1)

In the EU Directive 2001/20/EC on Clinical trials: "Adverse Event:" any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse event/Adverse experience (CIOMS VI)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adopted from: ICH Guideline E6: Good Clinical Practice

In the EU: "Adverse Event": any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

8. **Adverse event of special interest** (CIOMS VII)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (*e.g.*, regulators).

Adopted from: CIOMS VI Working Group

Commentary: An adverse event of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (*e.g.*, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instruction provided for investigators as to how and when they should be reported to the sponsor.

Adverse event of special interest (CIOMS VI)

{Synonym: Targeted medical event}

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid

communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (*e.g.*, regulators).

Proposed by CIOMS Working Group VI.

Commentary: An adverse event of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (*e.g.*, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor.

9. **Advocate / Patient advocate** (CIOMS IX)
{Synonym: Patient navigator}

A person who helps a patient work with others who have an effect on the patient's health, including doctors, insurance companies, employers, case managers, and lawyers. A patient advocate helps resolve issues about health care, medical bills, and job discrimination related to a patient's medical condition.

Adopted from: National Cancer Institute at the National Institutes of Health: Webpage, accessed 21 March 2014.

10. **Alert** (CIOMS VIII, also available in Chinese)
An identified risk associated with the use of medicinal products which requires urgent measures to protect patients.

Proposed by CIOMS Working Group VIII.

11. **Analysis of covariance (ANCOVA)** (CIOMS VI)
A statistical method for making comparisons between groups, while taking into account different variables measured at the start of a trial. It is a form of multiple regression.

Proposed by CIOMS Working Group VI.

B

12. **Baseline characteristics** (CIOMS DILI)
Factors that describe study participants at the beginning of the study (*e.g.*, age, sex, disease severity). In comparison studies, it is important that these characteristics be initially similar between groups; if not balanced or if the imbalance is not statistically adjusted, these characteristics can cause confounding and can bias study results.

Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

13. **Bayesian** (CIOMS VI)
A theorem in probability named after Reverend Thomas Bayes (1702-1761). It is used to refer to a philosophy of statistics that treats probability statements as having degrees of belief, in contrast to classical or Frequentist statistics that regards probability strictly as being based on frequencies of occurrence of events.

Proposed by CIOMS Working Group VI.

14. **Bayesian confidence propagation neural network (BCPNN)** (CIOMS VIII, also available in Chinese)
Empirical Bayesian algorithm used for signal detection in spontaneous report databases.
Proposed by CIOMS Working Group VIII.

15. **Benefit** (CIOMS IX)
An estimated gain for an individual or a population.
Adopted from: WHO 2002: The Importance of Pharmacovigilance. (Safety monitoring of medicinal products).

Benefit (CIOMS IV)
Benefit usually refers to a gain (positive result) for an individual or a population. ''Expected'' benefit can be expressed quantitatively, and this would ordinarily incorporate an estimate of the probability of achieving the gain. These uses of the term benefit are those employed in this report. Some current definitions of benefit include reference not only to clinical improvement but also to quality of life and economic consequences, as in the following example*:
''The improvement attributable to the drug, in terms of human health, health-related quality of life, and/or economic benefit to the individual or group.''
Proposed by CIOMS Working Group IV.

16. **Bias** (CIOMS X)
A systematic deviation in results from the truth.
Proposed by CIOMS Working Group X.

17. **Binary analysis** (CIOMS VI)
An analysis involving only two categories (*e.g.*, baseline vs final values, in contrast to analysis of multiple values from continuous measurements, as for a progression of laboratory values). The latter can be turned into a binary analysis by setting a single cut-off point so the data are split into just two possible values (*e.g.*, baseline vs highest post-baseline value).
Proposed by CIOMS Working Group VI.

18. **Biomarker** (CIOMS DILI)
A measured characteristic of either normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.
Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

Biomarker (CIOMS IX)
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Adopted from: Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001, 69: 89–95.

19. **Bonferroni correction** (CIOMS VI)
A correction to allow for the probability of many events that are independent, named after Carlo Emilio Bonferroni (1892-1960). In statistical significance testing, it allows, for example, 10 different significance tests to be made on a data set (*e.g.*, 10 different laboratory parameters) but still have an overall significance for one of the 10 tests at a probability of P=0.05, by carrying out each of the 10 tests by using a more stringent probability level of P=0.005 (thus, 0.05/10).
Proposed by CIOMS Working Group VI.

20. **Boxed warning**, synonym: Black box warning (CIOMS DILI)
A warning that appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks. Not all health authorities implement boxed warnings in the label, however some health authorities do (*e.g.*, those of the U.S., the United Kingdom and Japan). In the U.S., boxed warnings are ordinarily used to highlight for prescribers one of the following situations: (1) There is an adverse reaction so serious in proportion to the potential benefit from the drug (*e.g.*, a fatal, life-threatening or permanently disabling adverse reaction) that it is essential it be considered in assessing the risks and benefits of using the drug, OR (2) There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (*e.g.*, patient selection, careful monitoring, avoid certain concomitant therapy, addition of another drug or managing patient in a specific manner, avoiding use in a specific clinical situation), OR (3) FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (…) Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (*e.g.*, reduced effectiveness in certain patient populations). Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (*e.g.*, reduced effectiveness in certain patient populations).
Proposed by CIOMS DILI Working Group, partly based on: U.S. FDA. Guidance to Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format. October 2011. (PDF, accessed 29 March 2020)

21. **Burden of a risk minimisation activity** (CIOMS IX)
Burden is defined as the additional load that a risk minimisation activity imposes on (1) patients, (2) carers, (3) the healthcare system including health care professionals, (4) others such as regulatory authorities, pharmaceutical companies, the supply chain and those involved in access and supervision of the use of medicines.

The burden may impact, for example:

- Patients by adversely affecting their access to prescribed medicines and/or needed healthcare services, daily activities or routines;
- Healthcare providers by adding steps or services that are normally not required in the day-to-day management of their medical area;
- The health care system by requiring extra human and/or financial resources;
- Other entities of the healthcare system by including additional scientific evaluation of the risk minimization plan, its implementation, and its effectiveness.

Proposed by CIOMS Working Group IX.

C

22. **Candidate gene study** (CIOMS DILI)
A study that evaluates the association of specific genetic variants with outcomes or traits of interest, selecting the variants to be tested according to explicit considerations (known or postulated biology or function, previous studies, etc).
Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

23. **Case report form (CRF)** (CIOMS DILI)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Adopted from: ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice. E6(R2). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. (PDF)

Case report form (CIOMS VI)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Adopted from: ICH Guideline E6: Good Clinical Practice.

24. **Causality assessment** (CIOMS DILI)
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event in a specific individual. Causality assessment is usually made according to established algorithms.
Adopted from: CIOMS Working Group VIII.

Causality assessment (CIOMS VIII, also available in Chinese)
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event in a specific individual. Causality assessment is usually made according to established algorithms.
Modified from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala.

25. **Censored**/Censoring (CIOMS X)
An observation is said to be censored in time when the event of interest cannot be observed at the time at which the analysis is conducted. Special cases are right censoring when the observation has not yet been observed at the time of the analysis, left censoring when the observation occurred sometime before the observation period began, and interval censoring when the observation's time of occurrence has been recorded as within a time interval.
Proposed by CIOMS Working Group X.

Censored, or Censoring of data (CIOMS VI)
The act of eliminating data from analyses. Observations on certain patients, particularly the time until an event occurs, may be missing or incomplete. That is, the person has been followed for a

known length of time but the event of interest for analysis has not yet occurred. Such observations are called “censored” observations, and the process is called “censoring”.

Proposed by CIOMS Working Group VI.

26. **Channelling** (CIOMS X)

A situation where drugs are prescribed to patients differentially based on the presence or absence of factors prognostic of patient outcomes.

Adopted from: Guidance for Industry and FDA Staff:“Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data,” U.S. Food and Drug Administration, Center for Biologics and Evaluation and Research, Drug Safety, May 2013.

27. **Chi-square** (CIOMS VI)

This can refer to a statistical significance test or to the theoretical distribution to which a chi-square test refers (*i.e.*, chi-square distribution). The test is usually a comparison of proportions. In its simplest form, with a 2 x 2 contingency table, it is described as a one degree of freedom test. For example, a statistical comparison of the proportions of adverse reactions in two groups of patients is made using a chi-square test. The test results in a chi-square value from which a P value is obtained. This gives the probability of finding a difference in proportions as large as or larger than the difference observed, even when there is no true difference in those proportions. The data can have more than two treatments, and also more than two categories of response. Chi-square tests of data from larger size tables have higher numbers of degrees of freedom.

Proposed by CIOMS Working Group VI.

28. **CIOMS reportable case histories** (CIOMS reports) (CIOMS II)

Serious, medically substantiated, unlabeled adverse drug reactions about which there is sufficient information. Four pieces of information constitute a minimum report: an identifiable source of the information, a patient (even if not precisely identified by name and date of birth), a suspect drug, and a suspect reaction.

Proposed by CIOMS Working Group II.

29. **Clinical endpoint** (CIOMS IX)

A characteristic or variable that reflects how a patient feels, functions, or survives.

Adopted from: Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001, 69: 89–95.

30. **Clinical trial**/clinical study (CIOMS VII)

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms “clinical trial” and “clinical study” are synonymous.

Source: ICH E6 Guideline (GCP).

31. **Cohort event monitoring (CEM)** (CIOMS VIII, also available in Chinese)
A surveillance method that requests prescribers to report all observed adverse events, regardless of whether or not they are suspected adverse drug reactions, for identified patients receiving a specific drug. Also called prescription event monitoring.
Adopted from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala.

32. **Cohort study (prospective / retrospective)** (CIOMS IX)
Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies can be performed either prospectively, that is simultaneous with the events under study, or retrospectively, that is after the outcomes under study had already occurred, by recreating those past events using medical records, questionnaires, or interviews.
Adopted from: Strom, BL. Pharmacoepidemiology. 4th ed., Wiley. 2005, p. 23.

33. **Company core safety information (CCSI)** (CIOMS VII)
All relevant safety information contained in the Company Core Data Sheet prepared by the MAH (Marketing Authorisation Holder) and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.
Adopted from: ICH Guideline E2C: Periodic Safety Update Report of Marketed Drugs
Commentary: The CIOMS VI Working Group suggested that for drugs on the market in some places while under investigation in others, consideration should be given to using the CCSI as the basis for expedited reporting on cases arising in post-approval (Phase 4) clinical trials. See Chapter 7, section b.(3). of the CIOMS VI report.

Company core safety information (CCSI) (CIOMS VI)
All relevant safety information contained in the company core data sheet prepared by the MAH [Marketing Authorization Holder] and that the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.
Adopted from: ICH Guideline E2C: Periodic Safety Update Report for Marketed Drugs.
{The reports of CIOMS Working Groups III and V did not include formal glossaries but the concept of core safety information was discussed in the reports.}
Commentary: The CIOMS VI Working Group believes that for drugs on the market in some places while under investigation in others, consideration should be given to using the CCSI as the basis for expedited reporting on cases arising in post-marketing (Phase 4) clinical trials. See Chapter 7, section b.(3).

34. **Compassionate use** (CIOMS VII)
The use of an unapproved drug in an individual patient with a serious medical condition where the use of an unproven therapy is justified due to the lack of alternative safe and effective treatments.
Proposed by CIOMS Working Group VII.

Commentary: Some medical dictionaries define "compassionate use" as a method of providing experimental therapeutics prior to final regulatory approval for use in humans. This procedure is often used with very sick individuals who have no other treatment options. Often, case-by-case approval must be obtained from the regulatory authority for "compassionate use" of a drug or other therapy.

35. **Completed clinical trial** (CIOMS VII)

Study for which a final clinical study report is available.

Source: Proposed by CIOMS Working Group VII.

Commentary: As a reminder, ICH Guideline E3 (Structure and content of clinical study reports) is the template for final study reports in use by most commercial sponsors.

36. **Composite endpoint** (CIOMS X)

A composite endpoint is a single measure of effect, based on a combination of individual endpoints, each component being itself clinically meaningful. An example of a composite endpoint is MACE (Major Adverse Cardiac Event) which is typically a combination of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Proposed by CIOMS Working Group X.

37. **Confidence interval (CI)** (CIOMS VI)

An interval which shows the range of uncertainty in a measured summary value, such as a relative risk (RR). It is typically expressed as a 95% CI but it can be 99% or other value. If a 95% CI is from 0.26 to 0.96, it implies that the treated group shows evidence of a reduction in the event rate, but that the data are compatible with a large reduction (RR = 0.26) and also a small reduction (RR = 0.96). Strictly speaking, a 95% CI implies that 95% of such intervals, will, in the long run, contain the true value of the summary (in this example, the RR). The boundaries are the lower (0.26) and the upper (0.96) confidence interval. If the boundary includes the null value, such as an RR of 1, it means the difference is not statistically significant (*e.g.*, a CI of 0.5 to 1.8).

Proposed by CIOMS Working Group VI.

38. **Confounding** (CIOMS X)

Confounding occurs when a variable exists that influences the use of a drug or medical procedure (or its avoidance) and also alters the probability of an outcome, the association of which to the drug or procedure is under investigation.

Modified from: Boston University School of Public Health, MPH modules, ©2016, definition of confounding at web address.

39. **Confounding by indication** (CIOMS X)

Confounding by indication is a type of confounding bias that occurs when a symptom or sign of disease is judged as an indication (or a contraindication) for a given therapy and is therefore associated both with use of drug or medical procedure (or its avoidance) and with a higher probability of an outcome related to the disease for which the drug is indication (or contraindicated).

Adopted from: Miquel Porta, ed (2014) A Dictionary of Epidemiology (sixth ed.) Oxford University Press. ISBN-13: 978-0199976737.

40. **Context of use (COU)** (CIOMS DILI)

(EMA) Full, clear and concise description of the way a novel methodology is to be used and the medicine development related purpose of the use. The Context of Use is the critical reference point for the regulatory assessment of any qualification application.

Adopted from: EMA. Essential considerations for successful qualification of novel methodologies. 05 December 2017 EMA/750178/2017. (PDF)

(U.S. FDA) A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use.

Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

41. **Contingency Table** (CIOMS VI)

A table of data arranged in categories in rows and columns. The simplest is a two-by-two (2 x 2) table with 4 cells, but it could have any number of rows and columns.

Proposed by CIOMS Working Group VI.

42. **Core data sheet** (International prescribing information) (CIOMS II)

A document prepared by the pharmaceutical manufacturer, containing all relevant safety information, such as adverse drug reactions, which the manufacturer stipulates should be listed for the drug in all countries where the drug is marketed. It is the reference document by which "labeled" and "unlabeled" are determined and is therefore always included in a report.

Proposed by CIOMS Working Group II.

43. **Correlation** (CIOMS VI)

A measure of the relationship between two (or more) variables. A correlation coefficient, which measures the strength of a linear relationship, can range from -1 (perfect negative linear relationship) through zero (no linear relationship) to +1, a perfect positive relationship.

Proposed by CIOMS Working Group VI.

44. **Covariance** (CIOMS VI)

The statistical measure of the way that two variables vary in relation to each other. It is used in calculations of correlation and regression coefficients.

Proposed by CIOMS Working Group VI.

45. **Covariate** (CIOMS X)

A variable that is possibly predictive of the outcome under study. A covariate may be of direct interest to the study or it may be a confounding variable or effect modifier.

Adopted from: Miquel Porta, ed (2014) A Dictionary of Epidemiology (sixth ed.) Oxford University Press. ISBN-13: 978-0199976737.132

Covariate (CIOMS VI)

This is a variable that is examined as to how it relates to another variable. It usually refers to an explanatory (influential) variable, while the variable of interest is the response or outcome variable.

Proposed by CIOMS Working Group VI.

46. **Coverage,** see Reach (CIOMS IX)

47. **Cox model** (CIOMS VI)
A form of multivariable regression used in survival analysis, named after Sir David Cox who suggested the method in 1972. It can examine the effect of several explanatory variables on the time to occurrence of some outcome event such as an adverse reaction. It makes some assumptions about the effect of these explanatory variables on the outcome.
Proposed by CIOMS Working Group VI.

48. **Cross-sectional study, prevalence study**, see also Survey (CIOMS IX)
Study in which the prevalence of a variable (*e.g.* exposure, an event, a disease) is measured in a population at a given moment; this can also be termed a prevalence study. In pharmacoepidemiology, cross-sectional studies can be used to measure, for example:
– The prevalence of a disease or an event in a population;
– The prevalence of exposure to a risk factor such as the use of a drug.
Adopted from: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

49. **Crude pooling** (CIOMS X)
A method of combining data from a number of studies that ignores which study they came from, treating them as if they came from a single study.
Proposed by CIOMS Working Group X.

50. **Cumulative meta-analysis** (CIOMS X)
A meta-analysis in which studies are added one at a time in a specified order (*e.g.* according to date of publication or quality) and the results are summarized as each new study is added. In a graph of a cumulative meta-analysis, each horizontal line represents the summary of the results as each study is added, rather than the results of a single study.
Adopted from: Glossary of Terms in The Cochrane Collaboration. Available from PDF.

D

51. **Data lock point for DSUR** (CIOMS VII)
The date (month and day) designated as the annual cut-off for data to be included in a DSUR. It is based on the Development International Birth Date (DIBD).
Proposed by CIOMS Working Group VII.

Data lock-point (Cut-off date) (CIOMS II)
The date designated as the cut-off date for data to be incorporated into a particular safety update. On this date the data available to the author of the safety report are extracted for review and stored.

Proposed by CIOMS Working Group II.

52. **Data mining** (CIOMS DILI)
Any computational method used to automatically extract useful information from a large amount of data. Data mining is a form of exploratory data analysis.
Adopted from: CIOMS Working Group VIII.

Data mining (CIOMS VIII, also available in Chinese)
Any computational method used to automatically extract useful information from a large amount of data. Data mining is a form of exploratory data analysis.
Modified from: Hand, Manilla and Smyth. Principles of data mining. Cambridge, MA, USA. MIT Press, 2001.

53. **Designated medical event (DME)** (CIOMS VIII, also available in Chinese)
Adverse events considered rare, serious, and associated with a high drug-attributable risk and which constitute an alarm with as few as one to three reports. Examples include Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, anaphylaxis, aplastic anaemia and torsade de pointes.
Adopted from: Hauben M et al. The role of data mining in pharmacovigilance. Expert Opinion in Drug Safety, 2005, 4:929-948.

54. **Development core safety information (DCSI)** (CIOMS VII)
An independent section of an Investigator's Brochure (IB) identical in structure to the Company Core Safety Information (CCSI) that contains a summary of all relevant safety information that is described in more detail within the main body of the IB. It is the reference safety document that determines whether an ADR is listed or unlisted.
Adopted from: CIOMS Working Group VI.

Development core safety information (DCSI) (CIOMS VI)
An independent section of an Investigator's Brochure (IB) identical in structure to the Company Core Safety Information (CCSI) that contains a summary of all relevant safety information that is described in more detail within the main body of the IB. It is the reference safety document that determines whether an ADR is listed or unlisted.
Proposed by CIOMS Working Group VI, based on the report of CIOMS Working Groups III and V.

55. **Development international birth date (DIBD)** (CIOMS VII)
Date of first approval (or authorisation) for conducting an interventional clinical trial in any country.
Proposed by CIOMS Working Group VII.
{See also International birth date}

56. **Development pharmacovigilance and risk management plan (DPRMP)** or Development risk management plan (DRMP) (CIOMS VII)
A plan to conduct activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects of medicines during clinical trials. This plan should be initiated early and modified as necessary throughout the development process for a new drug or drug-use.
Adopted from: CIOMS Working Group VI.

Development pharmacovigilance and risk management plan (CIOMS VI)
A plan to conduct activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects of medicines during clinical trials. This plan should be initiated early and modified as necessary throughout the development process for a new drug or drug-use.
Proposed by CIOMS Working Group VI.

57. **Development safety update report (DSUR)** (CIOMS VII)
A periodic summary of safety information for regulators, including benefit-risk considerations, for a drug, biologic or vaccine under development or study, prepared by the sponsor of the clinical trial(s).
Modified from: CIOMS Working Group VI.
Commentary: A DSUR should serve as a summary of the safety experience in all clinical trials for a drug in development, including trials for new uses of an already approved drug (*e.g.* new dosage forms, indications, populations). In practice, it can serve as the foundation for any changes in the Investigator's Brochure and /or Development Core Safety Information (DCSI). The benefit-risk relationship mentioned in this definition does not refer to the traditional concept covering the product itself; rather, it refers to the ongoing estimation as to whether the subjects or patients are well served by continuing in a clinical trial or development programme. See Chapter I, Section c. for more discussion.

Development safety update report (DSUR) (CIOMS VI)
A periodic summary of safety information for regulators, including any changes in the benefit-risk relationship, for a drug, biologic or vaccine under development, prepared by the sponsor of all its clinical trials.
Proposed by CIOMS Working Group VI.
Commentary: A DSUR should serve as a summary of the safety experience in all clinical trials for a drug in development, including trials for new uses of an already approved drug (*e.g.*, new dosage forms, indications, populations). In practice, it can serve as the foundation for any changes in the Investigator's Brochure and/or Development Core Safety Information (DCSI). The CIOMS VI Working Group believes that the DSUR can serve as a platform for reconciling and harmonizing the currently different periodic reporting requirements for clinical trials in the US (IND Annual Report) and the EU (Annual Safety Report). For details, see Chapter 7. CIOMS Working Group VII, in progress as of this report, is dedicated to proposing details on the format, content and timing of such reports.

58. **Direct healthcare professional communication (DHPC)** (CIOMS IX)
A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product.

Adopted from: EU Guideline on good pharmacovigilance practices: Module XVI Risk-minimisation measures: selection of tools and effectiveness indicators (28 April 2014)

{The definition stems from the EU Guideline on good pharmacovigilance practices: Module XV Safety communication (Rev 1) EMA/118465/2012 (Rev 1, 9 October 2017) Originally it was included in Volume 9A of the Rules Governing Medicinal Products in the European Union, predating EU GVP.

{In the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017). the definition is slightly different:
"A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from health care professionals."}

59. **Disproportionality analysis**/Analysis of disproportionate reporting (CIOMS DILI)
The application of computer-assisted computational and statistical methods to large safety databases for the purpose of systematically identifying drug-event pairs reported at disproportionately higher frequencies relative to what a statistical independence model would predict.

Adopted from: CIOMS Working Group VIII.

Disproportionality analysis/Analysis of disproportionate reporting (CIOMS VIII, also available in Chinese)
The application of computer-assisted computational and statistical methods to large safety databases for the purpose of systematically identifying drug-event pairs reported at disproportionately higher frequencies relative to what a statistical independence model would predict.

Adopted from: Almenoff J et al. Perspectives on the use of data mining in pharmacovigilance. Drug Safety, 2005, 28:981-1007.

60. **Dominant risk** (CIOMS IV)
The risk that is considered to be the major contributor to the overall risk profile.

Note: Other terms used to describe the dominant risk are, *e.g.*, primary risk or risk driver. Dominant risk is the one adverse reaction that outweighs the others in the overall risk profile and risk management of the product.

Proposed by CIOMS Working Group IV.

61. **Drug-event pair** (CIOMS VIII, also available in Chinese)
A combination of a medicinal product and an adverse event which has appear in at least one case report entered in a spontaneous report database.

Proposed by CIOMS Working Group VIII.

E

62. **Ecological bias** (also known as Ecological fallacy) (CIOMS X)
An erroneous inference that may occur because an association observed between variables on an aggregate level does not necessarily represent or reflect the association that exist at an individual level.

Adopted from: Miquel Porta, ed (2014) A Dictionary of Epidemiology (sixth ed.) Oxford University Press. ISBN-13: 978-0199976737.

63. **Educational tool** (CIOMS IX)
Material designed to impart awareness, knowledge and aid comprehension of specific information.
Proposed by CIOMS Working Group IX.

64. **Effect modifier** (CIOMS X)
A feature of study individuals such that a treatment or risk factor has different effect at different levels of the feature, *i.e.* that there is an interaction between the feature and the treatment. The term is mostly used in an epidemiological context.
Adopted from: Dodge, Y, The Oxford Dictionary of Statistical Terms, 6th ed., International Statistical Institute, New York. Oxford University Press, Inc., 2006.

65. **Effectiveness** (CIOMS IX)
Extent to which an intervention when used under the usual clinical circumstances does what it is intended to do for a defined population.
Adopted from: Hartzema AG, Porta MS, Tilson HH. Pharmacoepidemiology: An introduction. 2nd Edition. Harvey Whitney Books. 1991.

Effectiveness (CIOMS VI)
Effectiveness is a measure of the effect a medicine (or medical technology) is purported, or is represented, to have under conditions for the use prescribed, recommended or labeled.
Proposed by CIOMS Working Group IV.
Commentary: The standard definition usually given in medical dictionaries is similar: the ability of an intervention to produce the desired beneficial effect in actual use.

Effectiveness (CIOMS IV)
Effectiveness is a measure of the effect a medicine (or medical technology) is purported, or is represented, to have under conditions for the use prescribed, recommended or labelled.
Note: Effectiveness refers to how well a drug achieves its intended effect in the usual clinical setting (''real world'') and reflects its impact in the community (benefits observed at the population level). [Footnote 2]

[Footnote 2 in the report:] Abramson, J.H., Survey Methods in Community Medicine, 4th Edition, p. 49. Churchill Livingstone, New York (1990); and Cochrane, A.L. Effectiveness and Efficiency, Random Reflections on Health Services. Nuffield Provincial Hospital Trust, London, 1972.
Proposed by CIOMS Working Group IV.

66. **Effectiveness of risk minimization** (CIOMS IX)
Measure of effect of risk minimisation in a setting allowing for meaningful conclusions with regard to the use of a medicinal product.
Proposed by CIOMS Working Group IX.

67. **Effectiveness threshold** (CIOMS IX)
Minimum acceptable level of risk minimisation to be achieved in order for the intervention to be rated a success. The effectiveness threshold is determined subjectively taking into account the impact of risk, the vulnerability of the target population, the drug's benefit in a given indication as well as aspects of practicality and feasibility.

Proposed by CIOMS Working Group IX.

68. **Efficacy** (CIOMS VI)
Efficacy is the ability of a medicine or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

Adopted from: CIOMS Working Group IV.

Commentary: Efficacy refers to how well a particular medicine causes the desired effect under ideal or near ideal conditions, as in a clinical trial setting. A drug is "efficacious" if it demonstrates the intended therapeutic effect under standardized/experimental conditions.

Efficacy (CIOMS IV)
Efficacy is the ability of a medicine or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

Note: Efficacy generally refers to how well a particular medicine will bring about the intended effect under ''ideal'' or near ideal conditions, as in a clinical-trial setting, for example.

Proposed by CIOMS Working Group IV.

69. **Efficiency** (CIOMS IX)
Results achieved in relation to the resources invested.

Adopted from: Hartzema AG, Porta MS, Tilson HH. Pharmacoepidemiology: An Introduction. 2nd Edition. Harvey Whitney Books. 1991.

70. **Endpoint** (CIOMS DILI)
A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

Endpoint (CIOMS X)
An endpoint (''target'' variable, outcome) is a measurement specified and designed to be capable of capturing the clinically relevant effects of an intervention, and to provide convincing evidence directly related to a specific objective of the meta-analysis.

Proposed by CIOMS X. Modified from ICH International Conference on Harmonisation. ICH E9 Statistical principles for clinical trials ICH Harmonised Tripartite Guideline. 1995.

71. **Epigenomics** (CIOMS DILI)
The study of all of the epigenetic changes in a cell. Epigenetic changes are changes in the way genes are switched on and off without changing the actual deoxyribonucleic acid (DNA) sequence. They may be caused by age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals. Epigenetic changes can affect a person's risk of disease and may be passed from parents to their children.
Adopted from: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage)

72. **Evaluation of drug-induced serious hepatotoxicity (eDISH) plot** (CIOMS DILI)
A log/log display of correlation between peak TBL vs. ALT, both in multiples of the upper limit of the normal range (ULN), with horizontal and vertical lines indicating Hy's law thresholds, *i.e.* ALT = 3 × ULN and total bilirubin = 2 × ULN. The eDISH plot makes immediately evident subjects potentially matching Hy's law laboratory criteria, all located in the upper right quadrant of the graph.
Proposed by CIOMS DILI Working Group, modified from: Merz M, Lee KR, Kullak-Ublick GA, Brueckner A, Watkins PB. Methodology to assess clinical liver safety data. Drug Saf. 2014;37(Suppl 1)S33–S45. (PMC full text, Journal full text)

73. **Expected and Unexpected adverse drug reaction** (See also Listed and Unlisted) (CIOMS VII)
An expected adverse drug reaction (ADR) is one for which its nature or severity is consistent with that included in the appropriate reference safety information (*e.g.*, Investigator's Brochure for an unapproved investigational drug or package insert/summary of product characteristics for an approved product).

An unexpected ADR is defined as: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.*, Investigator's Brochure for an unapproved investigational drug or package insert/summary of product characteristics for an approved product).

Adopted from: CIOMS Working Group VI.

Note: ICH does not define "expected adverse drug reaction."

In the EU: "Unexpected Adverse Reaction" – an adverse reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.*, investigator's brochure for an unauthorised investigational drug or summary of product characteristics for an authorised product).

Commentary: The concept of "expectedness" refers to events which may or may not have been previously observed and documented. It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the active substance.

Expected and Unexpected adverse drug reaction (CIOMS VI)
An expected adverse drug reaction (ADR) is one for which its nature or severity is consistent with that included in the appropriate reference safety information (*e.g.*, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Modified from: CIOMS Working Group V report, p. 109.

{The report of CIOMS WG V did not include a formal glossary but the concept of expectedness was discussed in several places in the report. Please see the report index.}

An unexpected ADR is defined as: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.*, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adopted from: ICH Guideline: E6 Good Clinical Practice

[Note: ICH does not define "expected" ADR.]

In the EU: "Unexpected Adverse Reaction" – an adverse reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.*, investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorised product).

Commentary: The concept of "expectedness" refers to events which may or may not have been previously observed and documented. It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the medicine. Depending on the context, expected and unexpected can refer to labeled vs unlabeled (for official data sheets/package inserts for marketed products) or listed vs unlisted (for the Investigator's Brochure, Development Core Safety Information (DCSI), or Company Core Safety Information (CCSI)). These other terms are also defined within this Glossary.

F

74. **Failure modes and effects analysis (FMEA)** (CIOMS IX)

Failure modes and effects analysis (FMEA) is a systematic method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change. FMEA includes review of the following:

- Steps in the process
- Failure modes (What could go wrong?)
- Failure causes (Why would the failure happen?)
- Failure effects (What would be the consequences of each failure?)

Modified from: Institute for Healthcare Improvement (IHI), Cambridge, Massachusetts, USA: Webpage, accessed Jun 16th, 2013.

75. **Fairweather Rules** (CIOMS VI)

Rules used by the FDA to analyze carcinogenicity studies. See Fairweather, W.R., et al., Biostatistical Methodology in Carcinogenicity Studies. *Drug Information Journal*, 32: 402-421 (1998).

76. **False negative** (CIOMS VI)

Usually used in connection with diagnostic testing, when a test result is negative in someone who actually does have the disease. It is also applied to statistical test results where a non-significant test result is found, whereas the null hypothesis (that there is no difference) is in fact false. The probability of this happening depends on the magnitude of the true difference. This magnitude can be assumed and the sample size in a study adjusted in order to ensure that the probability of a false negative is low. In studies of adverse reactions, it will often be high because the usual low incidence of ADRs makes finding significant differences difficult.

Proposed by CIOMS Working Group VI.

{See also: Type I and Type II errors}

77. **False positive** (CIOMS VI)
Usually used in connection with diagnostic testing, when a test result is positive in someone who does not have the disease. It is also applied to statistical test results where a significant test result occurs but the null hypothesis (no real difference) is in fact true. The probability of this happening can be set in advance by the analyst.
Proposed by CIOMS Working Group VI.
{See also: Type I and Type II errors}

78. **Fisher's exact test** (CIOMS VI)
An alternative to a chi-square test that is used when numbers in some cells are small. It gives a P value as its result.
Proposed by CIOMS Working Group VI.

79. **Fixed effects** (CIOMS X)
Fixed effects refer to one way in which the individual study estimates of treatment effect are combined in the meta-analysis. In a fixed-effect model the variability among the individual study estimates is not included in the analysis. The contribution of each study is usually determined only by the precision of each study. (See also Random effects)
Proposed by CIOMS Working Group X.

80. **Forest plot** (CIOMS X)
A forest plot is a graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. The weight of the study in the overall analysis is often represented by the area of a square plotted at the point estimate. A horizontal line runs through each square to show each study's confidence interval (CI) – usually, but not always, a 95% CI. The overall estimate from the meta-analysis and its CI are shown at the bottom, often represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the CI.
Modified from: Glossary of Terms in the Cochrane Collaboration. Available from PDF.

81. **Frequentist statistics** (CIOMS VIII, also available in Chinese)
Probabilities viewed as a long term frequency with an assumption of a repeatable experiment or sampling mechanism.
Proposed by CIOMS Working Group VIII.

G – H

82. **Genome-wide association study (GWAS)** (CIOMS DILI)
A study that evaluates the association of genetic variation with outcomes or traits of interest by using 100 000 to 1 000 000 or more markers across the genome.
Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

83. **Genomics** (CIOMS DILI)
The study of the complete set of deoxyribonucleic acid (DNA) (including all of its genes) in a person or other organism. Almost every cell in a person's body contains a complete copy of the genome. The genome contains all the information needed for a person to develop and grow. Studying the genome may help researchers understand how genes interact with each other and with the environment and how certain diseases, such as cancer, diabetes, and heart disease, form. This may lead to new ways to diagnose, treat, and prevent disease.
Adopted from: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage)

84. **Harm** (CIOMS IX)
Damage qualified by measures of frequency of occurrence, severity or duration.
Adopted from: Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety. 2007, 30: 825–830.

85. **Hazard** (CIOMS IX)
A situation or given factor that under particular circumstances could lead to harm. A source of danger.
Modified from: CIOMS Working Group IV.

Hazard (CIOMS VIII, also available in Chinese)
A situation that under particular circumstances could lead to harm. A source of danger.
Adopted from: CIOMS Working Group IV.

Hazard (CIOMS IV)
A situation that under particular circumstances could lead to harm. A source of danger.
Proposed by CIOMS Working Group IV.

86. **Healthcare professional (HCP)** (also: Health professional) (CIOMS IX)
A person who is qualified and trained to provide healthcare to humans. This includes doctors, physician assistants in some jurisdictions, nurses, dentists, pharmacists and midwives. For the purposes of reporting suspected adverse reactions the definition of healthcare professional additionally includes coroners and medically-qualified persons otherwise specified by local regulations.
Modified from: Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety. 2007, 30: 825–830 and ICH Harmonised Tripartite Guideline post-approval safety data management: Definitions and standards for expedited reporting E2D (Nov 2003).

87. **Heterogeneity** (CIOMS X)
Heterogeneity refers to differences among studies and/or study results. Heterogeneity can generally be classified in three ways: clinical heterogeneity, methodological heterogeneity and statistical heterogeneity [Reference 252]. Clinical heterogeneity refers to differences among trials in their patient selection (*e.g.* disease conditions under investigation, eligibility criteria, patient characteristics, or geographical differences), interventions (*e.g.* duration, dosing, nature of the control) and outcomes (*e.g.* definitions of endpoints, follow-up duration, cut-off points for scales). Methodological heterogeneity refers to the differences in study design (*e.g.* the mechanism of randomization) and in study conduct (*e.g.* allocation concealment, blinding, extent and handling

of withdrawals and loss to follow up, or analysis methods). Decisions about what constitutes clinical heterogeneity and methodological heterogeneity do not involve any calculation and are based on judgement. On the other hand, statistical heterogeneity represents a notion that individual studies may have results that are not numerically consistent with each other, and the variation is more than what is expected on the basis of sampling variability alone. Statistical heterogeneity may be caused by known clinical and methodological differences among trials, by unknown trial (clinical or methodological) characteristics, or it may be due to chance.

[Reference 252 in the report:] Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ, 1994, 309(6965): 1351-1355.

Proposed by CIOMS X. Combined and modified from:
Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ, 1994, 309(6965).
Berlin JA, Crowe BJ, Whalen E, Xia HA, Koro CE, Kuebler J. Meta-analysis of clinical trial safety data in a drug development program: answers to frequently asked questions. Clin Trials, 2013.

88. **Hy's law** (CIOMS DILI)

A term based on the observation by Dr Hyman Zimmerman that "drug-induced hepatocellular jaundice is a serious lesion", with mortality ranging from 10 to 50%. The term applies to patients who develop hepatocellular liver injury attributed to the suspect drug with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >3 x upper limit of normal (ULN) (or baseline levels if elevated) and have a total bilirubin > 2 x ULN, without significant initial cholestasis. This observation formed a basis for the development of the e-DISH plot by the U.S. FDA.

Proposed by CIOMS DILI Working Group, based on: U.S. FDA. Guidance for Industry. Drug-induced livery injury: premarketing clinical evaluation. (PDF)

I

89. **Identified risk** (CIOMS IX)

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include:

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 Apr 2014).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017), with a reference to ICH-E2F.}

Identified risk (CIOMS VIII, also available in Chinese)
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.

Adopted from: Guideline on Risk Management Systems for medicinal products for human use, Volume 9A of Eudralex, Chapter I.3, March 2007.

Identified risk (CIOMS VII)
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include:

– an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data

– an adverse reaction observed in well designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship

– an adverse reaction suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Adopted from: Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

90. **Idiosyncratic DILI (IDILI)** (CIOMS DILI)
{See also Intrinsic DILI}

A hepatic reaction to drugs that occurs in a small proportion of individuals exposed to a drug and is unexpected from the drug's pharmacodynamic and pharmacokinetic profile in humans. It is usually not dose-related, although a dose threshold of 50–100 mg/day is usually required, occurs in only a small proportion of exposed individuals (unpredictable) and exhibits a variable latency to onset of days to weeks and less frequently many months.

Proposed by CIOMS DILI Working Group, based on: European Association for the Study of the Liver, Clinical Practice Guideline Panel: Chair, Panel members, EASL Governing Board representative. EASL Clinical Practice Guidelines: Drug-Induced Liver Injury. J Hepatol.2019;70(6): 1222-61. (Journal full text)

91. **Implementation** (CIOMS IX)
One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). In this context implementation refers to the extent to which a programme is delivered as intended (see Implementation fidelity). There are both individual-level and programme-level measures of implementation.

Modified from: Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health. 1999, 89(9): 1322–7.

92. **Implementation fidelity** (CIOMS IX)
The degree to which an intervention or programme is delivered as intended.

Adopted from: Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation Science 2007, 2:40. (Webpage, accessed 10 November, 2013)

93. **Important identified risk** and Important potential risk (CIOMS IX)
An identified risk or potential risk that could impact on the benefit-risk profile of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Modified from:

ICH Harmonised Tripartite Guideline Periodic Benefit-Risk Evaluation Report (PBRER) E2C (R2) (Dec 2012).

{The first sentence comes from the ICH E2F guideline, Development safety update report (17 August 2010), which in turn adopted it from Volume 9A Rules Governing Medicinal Products in the EU.}

Important identified risk, Important potential risk or Important missing information (CIOMS VII)
An identified risk, potential risk, or missing information that could impact on the risk-benefit balance of the product or have implications for public health.

Adopted from: Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

94. **Important missing information,** see Missing information (CIOMS IX)

95. **Incidence** (CIOMS IX)
Number of new cases of an outcome which develop over a defined time period in a defined population at risk. In an epidemiologic sense incidence is a measure where the numerator refers to the number of events (counting only the initial event in each patient) and the denominator often refers to the total person-time at risk during exposure to the study drug.

Combined and modified from:
Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830.
Strom, BL. Pharmacoepidemiology. 4th ed., Wiley, 2005, p.395.

96. **Independent data-monitoring committee (IDMC),** or Data and safety monitoring board (DSMB), or Monitoring committee, or Data monitoring committee (DMC) (CIOMS VII)
An independent data-monitoring committee that may be established by the sponsor to assess, at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Adopted from: ICH Guideline for Good Clinical Practice E6(R1).

Commentary: Data monitoring committees/boards are referred to by several names and they may have different roles and responsibilities depending on the particular circumstances. For convenience and consistency, the CIOMS Working Group favours the term Data and Safety Monitoring Board (DSMB). DSMBs are responsible for monitoring and reviewing both safety and efficacy data, not just "critical study endpoints." For detailed discussion on DSMBs, see the Report of CIOMS Working Group VI, specifically Appendix 5 and the references in Chapter II, section b.

Independent data-monitoring committee (IDMC) or Data and safety monitoring board (DSMB), or Monitoring committee, or Data monitoring committee (CIOMS VI)
An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Adopted from: ICH Guideline E6: Good Clinical Practice.

Commentary: Data monitoring committees/boards are referred to by several names and they may have different roles and responsibilities depending on the particular circumstances. For convenience and consistency, the CIOMS Working Group favours the term Data and Safety Monitoring Board (DSMB). DSMBs are responsible for monitoring and reviewing both safety and efficacy data, not just "critical study endpoints." For detailed discussion on DSMBs, see Appendix 5 in this report and the references cited in Chapter 2, Section b.

97. **Independent ethics committee (IEC)** (See also Institutional review board) (CIOMS VII)
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in the trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in the ICH Guideline for Good Clinical Practice E6(R1).

Adopted from: ICH Guideline for Good Clinical Practice E6(R1).

{The last sentence in the original ICH guideline ends "…as described in this guideline." CIOMS VII substituted the name of the guideline.}

In the EU Directive 2001/20/EC on Clinical trials: "Ethics Committee" – an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

Independent ethics committee (IEC) (Also, see Institutional review board) (CIOMS VI)
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Adopted from: ICH Guideline E6: Good Clinical Practice.

In the EU: "Ethics Committee" – an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

98. **Indicator** (CIOMS IX)
An indicator provides evidence that a certain condition exists or certain results have or have not been achieved or provides a measure to determine the extent they have been achieved.
Modified from: Brizius, J. A., & Campbell, M. D. Getting results: A guide for government accountability. Washington, DC: Council of Governors Policy Advisors. 1991.

99. **Individual participant data** (CIOMS X)
Data that list the values of variables in the study grouped so that a set of values from a single participant can be identified. This term contrasts with summary level data in which all results are presented as functions of the individual participant data from which values pertaining to an individual cannot be retrieved by any further calculation.
Modified from: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Annex 1 to the Guide on Methodological Standards in Pharmacoepidemiology, 17 December 2015, EMA/686352/201. (Webpage)

100. **Informational tool** (CIOMS IX)
Material that is applied to bring attention or focus on information relevant to meeting risk minimization objectives.
Proposed by CIOMS Working Group IX.

101. **Informed consent** (CIOMS VI)
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Adopted from: ICH Guideline E6: Good Clinical Practice
In the EU: " Informed Consent" – decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.
Commentary: As specified in the Declaration of Helsinki (see Appendix 4, paragraph 22), a physician should obtain a subject's freely given consent preferably in writing. If the consent cannot be obtained in writing, "non-written consent must be formally documented and witnessed." Informed consent as applied to children and incapacitated participants requires special consideration; see the EU Clinical Trial Directive (Article 2J, 2001/20/EC), the Declaration of Helsinki (Appendix 4), the International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS, Geneva, 2002.

102. **Institutional review board (IRB)** (See also Independent ethics committee (IEC) (CIOMS VII)
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in the trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
Source: ICH Guideline for Good Clinical Practice E6(R1).

Commentary: IEC and IRB are generally used synonymously. However, depending on country or region, the term IRB may be used instead of IEC (or EC), especially if the term is specified in regulations or may be legally binding (*e.g.*, IRB in the U.S). There also may be slight differences between Ethics Committees and Institutional Review Boards. For detailed discussion, see Chapter II of the Report of CIOMS Working Group VI.

Institutional review board (IRB), see also Independent ethics committee (IEC) (CIOMS VI)
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Adopted from: ICH Guideline E6: Good Clinical Practice.

Commentary: IEC (EC) and IRB are generally used synonymously. However, depending on country or region, the term IRB may be used instead of IEC (or EC), especially if the term is specified in regulations or may be legally binding (*e.g.*, IRB in the U.S.). There also may be slight differences between Ethics Committees and Institutional Review Boards. For detailed discussion, see Chapter 2 of this CIOMS report.

{EC: Ethics committee}

103. **International birth date** (CIOMS II)
{See also Development international birth date (DIBD)}

The date on which the first regulatory authority to approve a particular drug for marketing has done so. The proposal is that the manufacturer's data are extracted for review of the particular drug every six months subsequently, and that all regulatory authorities that wish to have safety updates will accept the same cut-off date.

Proposed by CIOMS Working Group II.

104. **International prescribing information** (CIOMS II)
See Core data sheet.

Proposed by CIOMS Working Group II.

105. **Interventional clinical trial**, see also Non-interventional clinical trial (CIOMS VII)
An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (*e.g.*, preventive care, drugs, surgical procedures, behavioural treatments, etc.) to evaluate their effects on health-related outcomes.

Adopted from: WHO International Clinical Trials Registry Platform (ICTRP)
(http://www.who.int/ictrp/glossary/en/index.html)

{URL no longer current as of 7 May 2021}

106. **Intrinsic DILI** (CIOMS DILI)
{See also Idiosyncratic DILI}

Intrinsic DILI is typically dose-related and occurs in a large proportion of individuals exposed to the drug (predictable). Its onset is within a short time span (hours to days).

Proposed by CIOMS DILI Working Group, based on: European Association for the Study of the Liver, Clinical Practice Guideline Panel: Chair, Panel members, EASL Governing Board representative. EASL Clinical Practice Guidelines: Drug-Induced Liver Injury. J Hepatol.2019;70(6): 1222-61. (Journal full text)

107. **Investigational drug** (CIOMS VII)
The term "investigational drug" is used to refer to the product that is the object of experiment, whether it is a drug, biologic or vaccine.

Proposed by CIOMS Working Group VII.

Commentary: This term is chosen to distinguish it from the term "Investigational Medicinal Product," which refers in some regulatory settings (*e.g.*, EU) to all the treatments used in a trial: placebo, active comparators or the "experimental" product.

Investigational product (CIOMS VI)
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Adopted from: ICH Guideline E6: Good Clinical Practice

In the EU: "Investigational medicinal product" – a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Commentary: For purposes of this CIOMS report, for drugs in development the term "investigational product" refers to the experimental (unapproved) product.

K – L

108. **Kaplan-Meier** (CIOMS VI)
Named after two statisticians who developed a graphical and tabular method of analysing survival-type data, which is relevant to ADR data.

Proposed by CIOMS Working Group VI.

109. **Labelled or Unlabelled** (See also Expected and Unexpected adverse drug reaction) (CIOMS VII)
For a product with an approved marketing application, any reaction which is not mentioned in the official product information is "unlabelled." If it is included it is termed "labelled."

Adopted from: CIOMS Working Group VI..

Labelled or Unlabeled (also, see Expected and Unexpected adverse drug reaction) (CIOMS VI)
For a product with an approved marketing application, any reaction which is not mentioned in the official product information is unlabelled. If it is included, it is termed labelled.

Modified from: CIOMS Working Group V.

{The report of CIOMS WG V did not include a formal glossary but the concept of being labelled or unlabeled was discussed in the report. Please see the report index.}

110. **Labelling** (CIOMS DILI)

The definition of this term varies by regulatory jurisdiction. In EU legislation the term refers to the information given on the immediate or outer packaging. In other medicinal product legislation, including that of the US, labelling may refer more broadly to the approved content of product information (see Product information).

Adopted from: CIOMS Working Group IX.

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)}

Labelling (CIOMS IX)

The definition of this term varies by regulatory jurisdiction. In EU legislation the term refers to the information given on the immediate or outer packaging. In other medicinal product legislation, including that of the US, labelling may refer more broadly to the approved content of product information (see Product information).

Proposed by CIOMS Working Group IX, includes definition taken from EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

111. **Listed/Unlisted**, see also Expected and Unexpected adverse drug reaction (CIOMS VII)

Any reaction which is not included in the Development Company Core Safety Information within a company's core data sheet for an investigational or developmental product is "unlisted." If it is included it is termed "listed."

Modified from: CIOMS Working Group VI.

Commentary: The terms "listed" and "unlisted" were purposely adopted in ICH Guideline E2C (Periodic Safety Update Reports for Marketed Drugs) for use with internal company safety information documents, so as to distinguish them from the terms labelled and unlabelled, which should only be used in association with official "labelling," *i.e.*, the Summary of Product Characteristics (SPC) or Package Insert, and generally the regulator-approved data sheets for marketed products. The usage of listed/unlisted has been extended to the Development Core Safety Information (DCSI) as recommended in Guideline for Preparing Core Clinical-Safety Information on Drugs, Second Edition, CIOMS Working Group III/V, CIOMS, Geneva, 1999.

Listed or Unlisted (also, see Expected and Unexpected adverse drug reaction) (CIOMS VI)

Any reaction which is not included in the Company Core Safety Information within a company's core data sheet for a marketed product is unlisted. If it is included, it is termed listed.

Modified from: CIOMS Working Group V.

{The report of CIOMS WG V did not include a formal glossary but the concept of being listed or unlisted was discussed in the report. Please see the report index.}

Commentary: The terms listed and unlisted were purposely adopted in ICH Guideline E2C (Periodic Safety Update Reports for Marketed Drugs) for use with internal company safety information documents, so as to distinguish them from the terms labeled and unlabeled, which should only be used in association with official "labeling," *i.e.*, the Summary of Product Characteristics (SPC), Package Insert, and generally the regulator-approved data sheets for marketed products. The usage of listed/unlisted has been extended to the Development Core Safety Information (DCSI) as recommended in Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition, CIOMS Working Group III/V, CIOMS, Geneva, 1999

M

112. **Maintenance** (CIOMS IX)

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). At the individual level, it refers to the long-term results of an intervention (a minimum of six months following the last intervention contact).

At the setting level, Maintenance refers to the continuation (short-term) or institutionalization (long-term) of a programme (Goodman and Steckler, 1987)*. This is the extent to which intervention settings will continue a programme (and which of the original components of the intervention are retained or modified), once the formal research project and supports are withdrawn.

Modified from: Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), 497, San Francisco: Wiley, 2008.

**{ Goodman RM, Steckler AB. The life and death of a health promotion program: an institutionalization case study. Int Q Community Health Educ. 1987 Jan 1;8(1):5-22. doi: 10.2190/E5H5-3N0A-XN9N-FQ9X. PMID: 20841179.}*

113. **MedDRA (Medical Dictionary for Regulatory Activities)** (CIOMS VII)

MedDRA is a clinically validated medical terminology for regulatory authorities and the regulated pharmaceutical industry for utilisation in data entry, retrieval, evaluation and presentation, in both pre- and post-marketing phases of the regulatory process. It covers diseases, diagnoses, signs, symptoms, therapeutic indications, investigation names and qualitative results, as well as medical and surgical procedures, medical, social and family history. MedDRA is one of the standards required for the electronic transmission of ICSR (individual case safety reports). Recommendations on the use of MedDRA are set out in an ICH endorsed 'Points to consider' document, as updated from time to time.

Source: ICH Topic M1: Medical Terminology (MedDRA)

For more information see the website www.meddramsso.com/MSSOWeb/.

114. **Medication guide (Med guide or MG)** (CIOMS IX)

A paper handout intended for patients that are distributed as part of drug labeling at the point of dispensing of certain prescription medicines in the U.S. Medication Guides address issues that are specific to the safe and appropriate use of particular drugs and drug classes, and they contain FDA-approved information that can help patients avoid serious adverse events and assist health professionals in counseling patients about the correct use when prescribing or dispensing a drug.

Modified from: Webpage, accessed 17 March 2013.

115. **Meta-analysis** (CIOMS X)

The statistical combination of quantitative evidence from two or more studies to address common research questions, where the analytical methods appropriately take into account that the data are derived from multiple individual studies.

Proposed by CIOMS Working Group X.

Meta-analysis (CIOMS VI)

The process of summarising data from more than one study to obtain a single answer. There are various different statistical techniques to accomplish this, each of which makes slightly different assumptions.

Proposed by CIOMS Working Group VI

116. **Metabolomics** (CIOMS DILI)

The study of substances called metabolites in cells and tissues. Metabolites are small molecules that are made when the body breaks down food, drugs, chemicals, or its own tissue. They can be measured in blood, urine, and other body fluids. Disease and environmental factors, such as diet, drugs, and chemicals, can affect how metabolites are made and used in the body. Metabolomics may help find new ways to diagnose and treat diseases, such as cancer.

Adopted from: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage)

117. **Meta-regression** (CIOMS X)

A technique used in meta-analysis to explore the relationship between study characteristics (e.g. concealment of allocation, baseline risk, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Adopted from: Glossary of Terms in the Cochrane Collaboration. Available from Webpage.

118. **Missing information** (CIOMS IX)

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

It is noted that there is an ICH definition for important missing information, which is: critical gaps in knowledge for specific safety issues or populations that use the marketed product (see Annex IV, ICH-E2C (R2) Guideline).

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)}

{The EU GVP Annex I (Rev 4, October 2017) has additional information: "The change of the EU term, to name this concept "missing information" rather than "important missing information", is to be clear that in the EU a marketing authorisation cannot be granted if there are unacceptable gaps in knowledge, in accordance with Article 12 of Regulation (EC) No 726/2004 a marketing authorisation shall be refused if the quality, safety or efficacy are not properly or sufficiently demonstrated."}

Missing information (CIOMS VII)

Information about the safety of a medicinal product which is not available at the time of submission of the Risk Management Plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Adopted from: Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

119. **Model for end-stage liver disease (MELD)** (CIOMS DILI)

A numerical scale that is currently used by United Network for Organ Sharing for allocation of livers for transplantation. It is based on objective and verifiable medical data (international normalized ratio, serum total bilirubin level, and serum creatinine level [or dialysis]) that summarize a patient's risk of dying with cirrhosis while awaiting liver transplantation.

The MELD-Na score also incorporates the patient's serum sodium level.

Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

120. **Multidisciplinary safety management team (SMT)** (CIOMS VII)
A team established within a sponsor company, the composition of which will vary over time. The team is responsible for the timely review, assessment and evaluation of incoming safety data.
Source: From the report of CIOMS Working Group VI.

121. **Multi-item gamma Poisson shrinkage (MGPS)** (CIOMS VIII, also available in Chinese)
Empirical Bayesian algorithm used for signal detection in spontaneous report databases.
Proposed by CIOMS Working Group VIII.

122. **Multiplicity** (CIOMS VI)
The statistical problem caused by making multiple comparisons with a single set of data. Significance tests are affected by how many such tests are made.
Proposed by CIOMS Working Group VI.

N

123. **Negative predictive value (NPV)** (CIOMS DILI)
The proportion of those who tested negative who actually do not have a disease or condition.
Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

124. **Non-interventional clinical trial** (see also Interventional clinical trial) (CIOMS VII)
A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.
Adopted from: EU Directive 2001/20/EC on Clinical trials and detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, ENTR/CT 3 Revision 2 dated April 2006.
Commentary: Observational studies (usually retrospective examination and analysis of existing data from medical practice data bases) are often referred to as non-interventional studies.

125. **Null hypothesis** (CIOMS VI)
A statistical hypothesis that usually implies no difference between groups. For rates of adverse reactions this may imply a relative risk of 1.
Proposed by CIOMS Working Group VI.

126. **Number needed to harm (NNH)** (CIOMS DILI)
The number of individuals needed to be treated for some specified period of time in order that one person out of those treated would have one harmful event (during some specified time period). NNH is the inverse of the absolute risk difference between a treated and a control group.

For example, if the rate of a hepatic event is 5% in the treated group as opposed to 1% in a control group over one year of treatment, the difference is 4%. Thus, 25 people would need to be treated for one year to prevent one event (1/25 = 4%).

Modified from: CIOMS Working Group VI to include calculation (given in CIOMS VI under "Number needed to treat").

Number needed to harm (NNH) (CIOMS VI)
The number of individuals needed to be treated for some specified period of time in order that one person out of those treated would have one harmful event (again, during some specified time period). See NNT for calculation.

Proposed by CIOMS Working Group VI.

127. **Number needed to treat (NNT)** (CIOMS VI)
The number of individuals needed to be treated for some specified period in order that one person out of those treated should have the desired benefit/outcome, such as the prevention of a medical event under treatment (MI*, e.g.). NNT is the reciprocal of the difference in rates of the measured benefit, between a treated and a control group. For example, if the rate of death is 1% in the experimental group as opposed to 2% in a control group over one year of treatment, the difference is 1%. Thus, 100 people would need to be treated for 1 year to prevent 1 death (1/100 = 1%).

Proposed by CIOMS Working Group VI.

**{MI = myocardial infarction}*

O

128. **Odds ratio** (CIOMS DILI)
The odds of an event (such as death) in one group compared to the odds in a reference group. Odds are used in betting but have useful mathematical properties in analysis of binary data. For example, if there are 10 individuals studied and 2 experience an event, the probability is 2/10 = 0.2. The odds are 2:8 (2 have the event compared with 8 who do not). Therefore, the odds = 0.25. If these odds are compared with another group in whom the odds are different, say 0.125, then the odds ratio is 2 (0.25/0.125). With rare events the OR approximates the relative risk.

Adopted from: CIOMS Working Group VI

Odds ratio (CIOMS X)
The ratio of one "odds" divided by another, where the "odds" of an event is a proportion divided by one minus the proportion. The way that it is commonly estimated from sample data is illustrated in Annex II. Glossary case study.

Proposed by CIOMS Working Group X.

Odds ratio (OR) (CIOMS VI)
The odds of an event (such as death) in one group compared to the odds in a reference group. Odds are used in betting but have useful mathematical properties in analysis of binary data. For example, if there are 10 individuals studied and 2 experience an event, the probability is 2/10 = 0.2. The odds are 2:8 (2 have the event compared with 8 who do not). Therefore, the odds = 0.25.

If these odds are compared with another group in whom the odds are different, say 0.125, then the odds ratio is 2 (0.25/0.125). With rare events the OR approximates the relative risk.

Proposed by CIOMS Working Group VI.

129. **One-sided vs Two-sided testing** (CIOMS VI)

One-sided testing (also called one-tailed testing) refers to an analysis that allows for/examines an effect in one direction only (*e.g.*, an increase over a comparator). Two-sided testing accounts for changes in either direction. In most instances, as with comparisons of risk between different products, two-sided testing is preferred. For more detail, refer to the original definition.

Proposed by CIOMS Working Group VI.

130. **Ongoing clinical trial** (CIOMS VII)

Study where enrolment has begun, whether a hold is in place or analysis is complete, but without a final clinical study report available.

Proposed by CIOMS Working Group VII.

131. **Outcome** (CIOMS X)

Synonym for Endpoint (see Endpoint). See also "Composite endpoint".

Proposed by CIOMS Working Group X.

132. **Outcome indicators** (CIOMS IX)

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimisation measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (28 April 2014)

{EMA has abandoned this term in the GVP Module XVI Revision 3 (1 February 2021, draft for public consultation), as they now see e.g. knowledge and behaviour change also as outcomes of risk minimisation measures.}

133. **Over–the–counter (OTC) drug / medicine** (CIOMS IX)

Medicinal product available to the public without prescription.

Adopted from: Glossary of terms used in Pharmacovigilance. The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala. Webpage, accessed 17 March 2013.

P

134. **Package leaflet** (CIOMS IX)

Patient product information in the EU. A leaflet containing information for the user which accompanies the medicinal product [Directive 2011/83/EC Art 1(26)].

Modified from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014)

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

135. **Parametric** (CIOMS VI)
A form of statistical analysis that makes assumptions about the type of distribution of the data. *E.g.*, a t-test assumes a normal distribution of the data, and is referred to as a parametric test.
Proposed by CIOMS Working Group VI.

136. **Passive surveillance** (of spontaneous reports) (CIOMS DILI)
A surveillance method that relies on healthcare providers (and consumers in some countries) to take the initiative in communicating suspicions of adverse drug reactions that may have occurred in individual patients to a spontaneous reporting system.
Adopted from: CIOMS Working Group VIII.

→ See also Passive vaccine safety surveillance (TERMS AND DEFINITIONS — VACCINES)

Passive surveillance (of spontaneous reports) (CIOMS VIII, also available in Chinese)
A surveillance method that relies on healthcare providers (and consumers in some countries) to take the initiative in communicating suspicions of adverse drug reactions that may have occurred in individual patients to a spontaneous reporting system.
Proposed by CIOMS Working Group VIII.

137. **Periodic safety update report (PSUR)** (CIOMS IX)
{Synonym: Periodic benefit-risk evaluation report (PBRER)}
Format and content for providing an evaluation of the benefit-risk balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.
Modified from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).
In the EU GVP Annex I (Rev 4, October 2017), a note has been added to the definition: "In the EU, periodic safety update reports should follow the format described in GVP Module VII".}

138. **Pharmacoepidemiology** (CIOMS IX)
The application of epidemiologic methods, measurements, analysis and reasoning to the study of uses and effects, both intended and unintended, of medicinal products including biologicals and vaccines in defined human populations.
Proposed by CIOMS Working Group IX.

Pharmacoepidemiology (CIOMS VIII, also available in Chinese)
Study of the use and effects of drugs in large populations.
Adopted from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. (Webpage)
{Note: The link leads to the living online UMC glossary, where the definition read as follows as at 31 May 2021: "Pharmacoepidemiology: Branch of epidemiology (see above) dealing with the effects of medicines in populations."}

139. **Pharmacovigilance** (CIOMS DILI)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Adopted from: The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva, WHO, 2002. (PDF), accessed 19 August 2019.

Pharmacovigilance (CIOMS IX)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.

Adopted from: Glossary of terms used in Pharmacovigilance. The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala.

Pharmacovigilance (CIOMS VIII, also available in Chinese)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Adopted from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. (Webpage, accessed 11 December 2009).

Pharmacovigilance (CIOMS VII)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Adopted from: The Importance of Pharmacovigilance – Safety Monitoring of Medicinal Products, World Health Organization, 2002 (ISBN 92 4159 015 7), and ICH Guideline E2E, Pharmacovigilance Planning.

Commentary: There is some uncertainty concerning the phrase "any other drug-related problems." At least in the present context, the CIOMS Working Group VII understands the phrase to refer to issues that could affect the safety and safe use of medicines, such as medication errors and potential product quality issues including quality defects. The CIOMS Working Group VII endorses the use of the term "Pharmacovigilance" for clinical safety activities throughout the lifecycle of a medicinal product.

Pharmacovigilance (CIOMS VI)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Adopted from: The Importance of Pharmacovigilance – Safety Monitoring of Medicinal Products, World Health Organization 2002 (ISBN 92 4 1590157), and ICH Guideline E2E, Pharmacovigilance Planning (Step 4, November 2004).

Commentary: There is some uncertainty concerning the phrase "any other drug related problem." At least in the present context, the CIOMS Working Group understands the phrase to refer to issues that could affect the safety and safe use of medicines, such as medication errors and potential product quality issues (*e.g.*, glass particles in ampoules). The CIOMS Working Group endorses the use of the term pharmacovigilance for clinical safety activities during drug development as well as for marketed products.

140. **Pharmacovigilance system** (CIOMS IX)
In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

{In the EU GVP Annex I (Rev 4, October 2017), the general definition as adopted by CIOMS IX is included as a note that follows the EU-specific definition. The latter is: "A system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR 2001/83/EC Art 1(28d)]."}

141. **Phases of clinical studies (I-IV)** (CIOMS VII)

- Phase I (most typical kind of study: Human Pharmacology): Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials.
- Phase II (most typical kind of study: Therapeutic Exploratory): Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.
- Phase III (most typical kind of study: Therapeutic Confirmatory): Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit.
- Phase IV (variety of studies: Therapeutic Use): Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose response or safety studies, and studies designed to support use under the approved indication, *e.g.*, mortality/morbidity studies, epidemiological studies.

Adopted from: For all the above definitions – ICH Guideline E8: General Considerations for Clinical Trials.

Commentary: ICH Guideline E8 has proposed that studies be categorized according to their objectives (human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use) as distinct from the traditional concept based strictly on temporal phases of drug development. For example, human pharmacology studies (traditionally referred to as Phase I) can be and often are conducted throughout a product's lifetime (even though they are referred to as "Initial trials…" in the definition given). In some settings, other terms are used to categorize study types; for example, Phase IIA studies are sometimes referred to as "proof of concept studies," Phase IIB can refer to studies that establish proper dosing, and Phase IIIB refers to "peri-approval" studies (Phase IV-like studies initiated prior to drug approval). Depending on the product and nature of the programme, there may not be a sharp or distinct division between the various phases of trials.

The CIOMS Working Group believes that the ICH definition of Phase IV studies needs modification by deleting the expression "(other than routine surveillance)," which is not accurate, and by emphasizing that such studies should be limited to uses and conditions specified within the approved product information (SPC, Package Insert, etc.).

Phases of clinical studies (I – IV) (CIOMS VI)

- Phase I (Human Pharmacology): Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials.
- Phase II (Therapeutic Exploratory): Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.

– Phase III (Therapeutic Confirmatory) Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit.

– Phase IV (Therapeutic Use) Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose response or safety studies, and studies designed to support use under the approved indication, *e.g.*, mortality/morbidity studies, epidemiological studies.

Adopted from: For all the above definitions – ICH Guideline E8: General Considerations for Clinical Trials.

Commentary: As delineated above, ICH Guideline E8 has proposed that studies be categorized according to their objectives (human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use), as distinct from the traditional concept based strictly on temporal phases of drug development. For example, human pharmacology studies (traditionally referred to as Phase I) can be and often are conducted throughout a product's lifetime (even though they are referred to as "Initial studies." in the definition above). In some settings, other terms are used to categorize study types; for example, Phase IIA studies are sometimes referred to as "proof of concept studies," Phase IIB can refer to studies that establish proper dosing, and Phase IIIB refers to "peri-approval" studies (Phase 4-like studies initiated prior to drug approval). Depending on the product and nature of the program, there may not be a sharp or distinct division between the various Phases of trials. Phase IV studies may be required as a condition of regulatory approval. The CIOMS Working Group believes that the ICH definition of Phase IV studies needs modification by deleting the expression "(other than routine surveillance)," which is not accurate, and by emphasizing that such studies should be limited to uses and conditions specified within the approved data sheet (SPC, Package Insert, etc.).

142. **Point estimate** (CIOMS VI)

The best estimate of a summary of data such as a mean or a relative risk. The value of this figure on its own does not indicate how precisely it is estimated.

Proposed by CIOMS Working Group VI.

143. **Positive predictive value (PPV)** (CIOMS DILI)

The proportion of those who tested positive who actually have a disease or condition.

Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

144. **Poisson distribution** (CIOMS VI)

A distribution of numbers, as in a normal distribution, but which applies to counts of numbers of events rather than to continuous values and is asymmetric. Negative values cannot occur.

Proposed by CIOMS Working Group VI.

145. **Post-authorization** (CIOMS VIII, also available in Chinese)

The stage in the life-cycle of a medicinal product that follows the granting of the marketing authorization, after which the product may be placed on the market.

Proposed by CIOMS Working Group VIII.

146. **Post-authorisation safety study (PASS)** (CIOMS IX)
Any study relating to an authorised medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014) [Directive 2001/83/EC Art 1(15)].

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017)}

{In the EU GVP Annex I (Rev 4, October 2017), there is an additional note to the definition: "A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design."}

147. **Post-marketing** (CIOMS DILI)
The stage when a drug is approved and generally available on the market.

Adopted from: Uppsala Monitoring Centre (UMC). Glossary of pharmacovigilance terms (Webpage, accessed 29 March 2020)

Post-marketing (CIOMS VIII, also available in Chinese)
The stage when a drug is available on the market.

Adopted from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala.

148. **Post-marketing surveillance** (CIOMS VIII, also available in Chinese)
Monitoring for adverse reactions to marketed products.

Modified from: Glossary of MHRA terms. (Webpage, accessed December 2020)

149. **Potential risk** (CIOMS IX)
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include:

- toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of, but is not large enough to suggest a causal relationship;
- a signal arising from a spontaneous adverse reaction reporting system;
- an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

{The first sentence of the definition is unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017), as well as the ICH E2F Guideline: Development Safety Update Report (17 August 2010). In both these documents the examples are worded slightly differently than in the CIOMS IX definition.}

Potential risk (CIOMS VIII, also available in Chinese)
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

Adopted from: Guideline on Risk Management Systems for medicinal products for human use, Volume 9A of Eudralex, Chapter I.3. (Webpage, accessed December 2020)

Potential risk (CIOMS VII)
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where an association has not been confirmed. Examples of potential risk include:

– non-clinical safety concerns that have not been observed or resolved in clinical studies
– adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance) or unexposed group, on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship
– a signal arising from a spontaneous adverse reaction reporting system
– an event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

Adopted from: Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

The CIOMS Working Group VII endorses this meaning as applied in this report.

150. **Power** (CIOMS VI)
In statistical terms, a measure or indication of whether an analysis that is conducted is good at detecting differences. A powerful analysis is one that finds differences to be statistically significant. Power largely depends on how many events are observed, which therefore depends both on how many individuals are studied (the more studied, the greater the power) and on the rarity of the event (the less there are, the less powerful).

Proposed by CIOMS Working Group VI.

151. **Pre-authorization** (CIOMS VIII, also available in Chinese)
{Synonym: Pre-marketing}
The stage in the life-cycle of a medicinal product before the drug has obtained a marketing authorization.

Note: A marketing authorization pertains to each indication. Once authorized for one indication, a drug still may be in pre-authorization development for another indication.

Adopted from: ICH Topic E8. General Considerations for Clinical Trials. 17 July 1997. (Webpage, accessed 11 December 2009)

152. **Pre-marketing** (CIOMS DILI)
The developmental stage before a drug is approved and available for prescription or sale to the public.

Adopted from: Uppsala Monitoring Centre (UMC). Glossary of pharmacovigilance terms (Webpage, accessed 29 March 2020.

Pre-marketing (CIOMS VIII, also available in Chinese)
The stage before a drug is available for prescription or sale to the public. Usually synonymous with pre-approval or pre-authorization.
Adopted from: Glossary of terms used in Pharmacovigilance, WHO Collaborating Centre for International Drug Monitoring, Uppsala.

153. **Prescription event monitoring (PEM)** or Cohort event monitoring (CEM) (CIOMS VIII, also available in Chinese)
A surveillance method that requests prescribers to report all observed adverse events, regardless of whether or not they are suspected adverse drug reactions, for identified patients receiving a specific drug. Also more accurately named "cohort event monitoring".
Adopted from: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala.

154. **Prevalence** (CIOMS DILI)
Number of existing cases of an outcome in a defined population at a given point in time. Note. Prevalence is calculated as a proportion (cases divided by total in population), often expressed as a percentage.
Adopted from: Uppsala Monitoring Centre (UMC). Glossary of pharmacovigilance terms (Webpage, accessed 29 March 2020)

Prevalence (CIOMS IX)
Number of existing cases of an outcome in a defined population at a given point in time.
Modified from: Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830.
Prevalence focuses on existing states. Prevalence of a state at a point in time may be defined as the proportion of a population in that state at that time.
Adopted from: Rothman KJ, Green land S, Lash T. Modern Epidemiology.3rd edition. Lippincott Williams & Wilkins. 2008:46.

155. **Primary endpoint** (CIOMS X)
The primary endpoint is the endpoint or outcome that defines the primary objective of a meta-analysis. (See also: Endpoint, Composite endpoint, and Outcome.)
Proposed by CIOMS Working Group X.

156. **Process indicators** (CIOMS IX)
Process indicators are measures of the extent of implementation of the original risk minimisation plan, and/or variations in its delivery.
Modified from: EU Guideline on good pharmacovigilance practices: Module XVI Risk-minimisation measures: selection of tools and effectiveness indicators (28 April 2014).
{EMA has abandoned this term in the EU GVP Module XVI Revision 3 (1 February 2021, draft for public consultation), as they now see e.g. knowledge and behaviour change also as outcomes of risk minimisation measures.}

157. **Product information (PI)** (CIOMS DILI)
Documents proposed by marketing authorisation holders / applicants, amended if required and agreed by regulatory authorities, which provide information to prescribers / healthcare professionals or patients on the appropriate and safe use of a medicinal product. As such the product information constitutes the main tool used for routine risk minimisation. For examples regarding terminology used in different regulatory jurisdictions see Fig. 1.1 in Chapter I of the CIOMS IX report [reproduced below]. The EU labelling on the immediate or outer packaging is a part of product information.

Figure 1.1 from CIOMS IX report: Examples of nomenclature for components of product information

PRODUCT INFORMATION (PI)

Product information for HCPs*	Product information for patients
• Summary of product characteristics (SmPC, also sometimes SPC) • Data sheet • Drug data sheet • Safety data sheet • Package insert • Product information	• Package leaflet • Patient information leaflet • Patient product information • Patient information • Consumer medicines information • Patient instructions for use • Patient package insert

Labelling on inner and outer packaging

*{*HCPs=health care professionals}*

Adopted from: CIOMS Working Group IX.

Product information (PI) (CIOMS IX)
Documents proposed by marketing authorisation holders / applicants, amended if required and agreed by regulatory authorities which provide information to prescribers / healthcare professionals or patients on the appropriate and safe use of a medicinal product. As such the product information constitutes the main tool used for routine risk minimisation. For examples regarding terminology used in different regulatory jurisdictions see Fig. 1.1 in Chapter I. The EU labelling on the immediate or outer packaging is a part of product information.

Figure 1.1: Examples of nomenclature for components of product information

{As shown above under Product information (PI) (CIOMS DILI)}

Proposed by CIOMS Working Group IX.

158. **Proportional reporting ratio (PRR)** (CIOMS VIII, also available in Chinese)
The proportion of reports for an event that involve a particular drug compared to the proportion of reports of this event for all drugs in a spontaneous report database. This is expressed as a ratio and reflects the observed/expected values for that event in the database.

Modified from: Evans SJW et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiology and Drug Safety 2001, 10:483-486.

159. **Proteomics** (CIOMS DILI)
The study of the structure and function of proteins, including the way they work and interact with each other inside cells.

Adopted from: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage)

160. **Protocol-related adverse event** (CIOMS VII)
An adverse event that is thought to be related to an aspect of a procedure or measurement as specified within the clinical trial protocol, but not directly or solely related to the administration of the drug or drugs under investigation.
Proposed by CIOMS Working Group VII.

Q

161. **Qualification** (CIOMS DILI)
A conclusion, based on a formal regulatory process, that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.
Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

162. **Qualitative signal detection** (CIOMS VIII, also available in Chinese)
Case-by-case manual screening of each individual case report of a suspected adverse drug reaction submitted to a spontaneous reporting system that must be performed by an assessor. The assessor uses his/her human intellect to evaluate the likelihood that the adverse event was caused by the suspect drug.
Modified from: Egberts TCG. Signal Detection: Historical Background. Drug Safety 2007, 30:607-609.

163. **Quantitative signal detection** (CIOMS VIII, also available in Chinese)
Refers to computational or statistical methods used to identify drug-event pairs (or higher-order combinations of drugs and events) that occur with disproportionately high frequency in large spontaneous report databases.
Adopted from: Almenoff J et al. Perspectives on the use of data mining in pharmacovigilance. Drug Safety, 2005, 28:981-1007.

R

164. **Random effects** (CIOMS X)
Random effects refers to one of the two ways in which the individual study estimates of treatment effect are combined in the meta-analysis. In a random-effects meta-analysis model the variability among the individual study estimates is included in the analysis. Thus, the contribution of each study to the overall estimate is usually determined by both the precision within each study and the among-study variability. (See also Fixed effects.)
Proposed by CIOMS Working Group X.

165. **Rank** (CIOMS VI)
The order of a value in a set of values. Some statistical methods (nonparametric tests) use the order rather than the actual value. In survival analysis the ordering of times is important and a "log rank test" is able to compare times to an event that occurs in different groups.

Proposed by CIOMS Working Group VI.

166. **Reach** (CIOMS IX)

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance), also referred to as 'coverage' or 'distribution'. Reach refers to the percentage of potential participants who are exposed to an intervention and how representative they are.

Adopted from: Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), 496, San Francisco: Wiley, 2008.

167. **Real-world data (RWD)** (CIOMS DILI)

Data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources. Examples of real-world data include the following: Data derived from electronic health records; medical claims and billing data; data from product and disease registries; patient-generated data, including in-home use and/or other decentralized settings; data gathered from other sources that can inform on health status, such as mobile devices.

Adopted from: U.S. Food and Drug Administration (FDA). Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics. Guidance for Industry. May 2019. (PDF)

168. **Receiver-operating characteristic (ROC) curve** (CIOMS DILI)

A figure depicting the power of a diagnostic test. The receiver operating characteristic (ROC) curve presents the test's true-positive rate (*i.e.*, sensitivity) on the horizontal axis and the false-positive rate (*i.e.*, 1 – specificity) on the vertical axis for different cut points dividing a positive from a negative test result. An ROC curve for a perfect test has an area under the curve of 1.0, whereas a test that performs no better than chance has an area under the curve of only 0.5.

Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

169. **Reference risk (baseline risk)** (CIOMS IX)

Risk measured in a population, called the reference population, which resembles the exposed population in all respects except that its members have not been exposed to the factor under study. The reference risk can be very different from the risk measured in the general population.

Adopted from: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

170. **Registry** (CIOMS DILI)

(Europe) An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Adopted from: European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP). Annex I - Definitions (Rev 4). 9 October 2017. (PDF)

(United States) A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.

Adopted from: Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide {Internet}. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 1, Patient Registries.

Registry (CIOMS IX)
An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Registry (CIOMS VII)
A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardised questionnaires in a prospective fashion.
Adopted from: ICH Guideline E2E, Pharmacovigilance Planning.
Commentary: Exposure (drug) registries address populations exposed to drugs of interest (*e.g.*, a registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposure in specific populations, such as pregnant women; however, pregnancy registries exist without any particular exposure in mind. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly of rare outcomes. This type of registry can be very valuable.

171. **Regression** (CIOMS VI)
A statistical technique that examines relationships between a response variable and one or more explanatory variables. This can be done for continuous measurements but also for binary measures and survival times.
Proposed by CIOMS Working Group VI.

172. **Relative risk** (CIOMS X)
A general term used to refer to relative measures of the magnitude of effect of the intervention or risk factor on the outcome, such as hazard ratio, odds ratio, risk ratio or rate ratio.
Proposed by CIOMS Working Group X.

Relative risk (RR) (CIOMS VI)
A multiplicative factor applied to a reference risk associated with an exposure. It is the risk of an outcome (event) measured in an exposed population (absolute risk) divided by the risk (reference risk) of the same outcome (event) in an unexposed group (the reference population).
Combined and modified from:
Report of CIOMS Working Group IV.
Dictionary of Pharmacoepidemiology, by B. Begaud, John Wiley & Sons, 2000.
Commentary: The relationship between two risks, generally estimated in different populations, is often referred to as the "risk ratio" as well as relative risk. There is a need to ensure that the two populations that are compared are "comparable" (*i.e.*, same/similar kinds of patients, age, gender, disease state, exposure time, etc.). Example: risk of adverse drug reaction (ADR) is 10/100,000 in drug-treated population and 5/1,000,000 in a comparable but untreated population. Relative risk = 20.

Relative risk (CIOMS IV)
The ratio of the incidence rate of an outcome (event) in an exposed group to the incidence rate of the outcome (event) in an unexposed group.

Adopted from: B.L. Strom, ed., Pharmacoepidemiology. John Wiley and Sons, New York, 1994.

173. **Reporting odds ratio (ROR)** (CIOMS VIII, also available in Chinese)
The odds (probability/1-probability) of finding an adverse event term among all case reports that mention a particular drug divided by the odds of finding the same adverse event term among all other case reports in the spontaneous report database that do not mention this drug.

Proposed by CIOMS Working Group VIII.

174. **Restricted access programme**, also known as Managed/Controlled access in some jurisdictions (CIOMS IX)
Restricted access programmes aimed at medicinal product risk minimisation consist of interventions seeking to restrict access to a medicine on the market beyond the level of control ensured by routine risk minimisation measures.

Examples of interventions that can be linked to restricted access programmes, alone or in combination may include:

- Documentation of specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria before the patient can receive the medication;
- Documentation of prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk/s associated with the medicinal product;
- Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system *e.g.* patient registry;
- The medicine being made available for dispensing only through pharmacies or other appropriate distribution channels that are registered and approved to dispense the medicinal product (controlled distribution).

Note: Since restricted access programmes for risk minimisation have significant implications and possible burden for all concerned stakeholders, their use should be limited and guided by a clear therapeutic need for the medicinal product based on its demonstrated benefit-risk profile, the nature of the associated risk and whether this risk is expected to be managed by additional risk minimisation interventions.

Modified from: EU Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (21 February 2014).

175. **Risk** (CIOMS IX)
The probability of developing undesirable outcomes relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health or any undesirable outcomes with regard to the environment.

Combined from:
Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830.
EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Risk (CIOMS VIII, also available in Chinese)
The probability of developing an outcome.

Note: The term risk normally, but not always, refers to a negative outcome. When used for medicinal products, the concept of risk concerns adverse drug reactions. Contrary to harm, the concept of risk does not involve severity of an outcome. The time interval at risk should be specified.

Modified from: Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30:825-830.

Risk (CIOMS VI)
{Synonym in CIOMS VI: Absolute risk}
As used in the context of adverse experiences, it is the proportion of individuals who have an event out of all those who could possibly have that event. Two groups can be compared either by taking their ratio (relative risk) or by subtracting the two risks. The latter is called an absolute risk difference.
Proposed by CIOMS Working Group VI.

Risk (CIOMS IV)
The simple, standard, epidemiological definition of risk is the probability that something will happen.
Note: In the context of medical interventions (drugs, *e.g.*), the ''something'' is almost always associated with a negative event. In defining or describing a specific risk, it is always important to include information on intensity (severity, *e.g.*), time of the event (onset or duration), and time period over which the probability applies. Some definitions attempt to include concepts of rate, intensity and time: The probability of the occurrence of an adverse or untoward outcome and the severity of the resultant harm to the health of individuals in a defined population, associated with the use of a medical technology for a specified medical problem under specified conditions of use.
Proposed by CIOMS Working Group IV.

176. **Risk assessment** (CIOMS IX)
Risk assessment consists of identifying and characterising the nature, frequency, and severity of the risk associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a potential product, through the pre-marketing development process, and after approval during marketing.
Note: Risk assessment can be subdivided into risk estimation and risk evaluation.
Adopted from: FDA Guidance for Industry. Premarketing Risk Assessment. March 2005.

Risk assessment (CIOMS VIII, also available in Chinese)
Risk assessment consists of identifying and characterizing the nature, frequency, and severity of the risk associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a potential product, through the pre-marketing development process, and after approval during marketing.
Adopted from: FDA Guidance for Industry. Premarketing Risk Assessment. March 2005.
Note: Risk assessment can be subdivided into risk estimation and risk evaluation.

Risk assessment (CIOMS VI)
Risk assessment is subdivided into risk estimation and risk evaluation. It is defined as the integrated analysis of the risks inherent in a product, system or plant and their significance in an appropriate context. Risk estimation includes the identification of outcomes, the estimation of the magnitude of the associated consequences of these outcomes and the estimation of the probabilities of these outcomes. Risk evaluation is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the decision. It therefore includes the study of risk perception and the trade-off between perceived risks and perceived benefits. It is defined as the appraisal of the significance of a given quantitative (or where acceptable, qualitative) measure of risk.
Adopted from: Risk analysis, perception and management. The Royal Society UK, 1992

177. **Risk avoidance** (CIOMS IX)
An informed decision not to become involved in activities that lead to the possibility of the risk being realized.
Adopted from: Risk Management and Decision Making Glossary.

178. **Risk-benefit balance** (CIOMS IX)
An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, *i.e.* any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

179. **Risk communication** (CIOMS IX)
Any exchange of information concerning the existence, nature, form, severity or acceptability of health or environmental risks. Effective risk communication involves determining the types of information that interested and affected parties need and want, and presenting this information to them in a useful, accessible and meaningful way.
Adopted from: Decision-making framework for identifying, assessing and managing health risks, Health Canada, 1 August 2000. (Webpage, accessed 11 December 2009)
Note: The Erice Declaration on Communicating Drug Safety Information lays out key principles for ethically and effectively communicating information on identified or potential risks. See Current Challenges in Pharmacovigilance: Report of CIOMS Working Group V. Geneva, Switzerland: CIOMS. 2001. Appendix 1: 219–220.

Risk communication (CIOMS VIII, also available in Chinese)
Any exchange of information concerning the existence, nature, form, severity or acceptability of health or environmental risks. Effective risk communication involves determining the types of information that interested and affected parties need and want, and presenting this information to them in a useful and meaningful way.
Adopted from: Decision-Making Framework for Identifying, Assessing and Managing Health Risks. Health Canada, 1 August 2000. (Webpage, accessed 11 December 2009).
Note: The Erice Declaration on Communicating Drug Safety Information lays out key principles for ethically and effectively communicating information on identified or potential risks. See Current Challenges in Pharmacovigilance: Report of CIOMS Working Group V. Geneva, CIOMS, 2001. Appendix 1, pp. 219-220.

180. **Risk difference** (CIOMS X)
The difference between two proportions. For more detail, refer to the original definition.
Proposed by CIOMS Working Group X.

181. **Risk elimination** (CIOMS IX)
'Absolute' or complete prevention of risk, *i.e.* reduction of the frequency of an undesirable outcome to zero.
Proposed by CIOMS Working Group IX.

182. **Risk estimation** (CIOMS IX)
Risk estimation includes the identification of outcomes, the estimation of the magnitude of the associated consequences of these outcomes and the estimation of the probabilities of these outcomes.
Adopted from: Risk analysis, perception and management, The Royal Society, UK. 1992.

183. **Risk evaluation** (CIOMS VIII, also available in Chinese)
Risk evaluation is the complex process of determining the significance of value of the identified hazards and estimated risks to those concerned with or affected by the decision. It therefore includes the study of risk perception and the trade-off between perceived risks and perceived benefits. It is defined as the appraisal of the significance of a given quantitative (or where acceptable, qualitative) measure of risk.
Adopted from: Risk analysis, perception and management, The Royal Society, UK. 1992.

Risk evaluation (CIOMS IV)
Risk evaluation is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the process.
Modified from: Risk analysis, perception and management, The Royal Society, UK. 1992.

184. **Risk evaluation and mitigation strategy (REMS)** (CIOMS DILI)
A drug safety programme that the U.S. FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.
Adopted from: U.S. FDA website. Risk Evaluation and Mitigation Strategies (REMS). Updated 8 August 2019. (Webpage)

REMS (Risk evaluation and mitigation strategy) (CIOMS IX)
FDA enforceable document required when necessary to ensure that the benefits of a drug outweigh the risks. It describes the elements that an applicant is required to implement.
Modified from: FDA Draft Guidance for Industry 'Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications' (Webpage, accessed December 2020)

185. **Risk factor** (CIOMS DILI)
Characteristics associated with an increased probability of occurrence of an event or disease.
Adopted from: CIOMS Working Group IX.

Risk factor (CIOMS IX)
Characteristics associated with an increased probability of occurrence of an event or disease.
Adopted from: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

186. **Risk identification** (CIOMS IX)
Determining what risks or hazards exist or are anticipated, their characteristics, remoteness in time, duration period, and possible outcomes.
Adopted from http://www.businessdictionary.com/definition/risk-identification.html, accessed 16 June 2013.
{Link no longer current as of May 2021}

187. **Risk level / Level of risk** (CIOMS IX)
Characterisation of an undesirable outcome by severity and likelihood of occurrence.
Proposed by CIOMS Working Group IX.

188. **Risk management** (CIOMS IX)
Reiterative activities or interventions associated with the identification, characterisation, prevention or mitigation of risks and the measurement of the effectiveness of the risk minimisation measures.
Proposed by CIOMS Working Group IX.

Risk management (CIOMS VI)
Risk Management is the making of decisions concerning risks and their subsequent implementation, and flows from risk estimation and risk evaluation. It is defined as the process whereby decisions are made to accept a known or assessed risk and/or the implementation of actions to reduce the consequences or probability of occurrence.
Adopted from: Risk analysis, perception and management. The Royal Society, UK, 1992.
Commentary: In the field of drug safety there is no accepted, universal definition of "risk management," but in current usage, it refers to the overall process for the technical and communication activities needed to understand and prevent or minimize risk/harm, including the assessment of any programs put in place. The US FDA refers to risk management as the combination of risk assessment and risk minimization (see the Guidance for Industry. Development and Use of Risk Minimization Action Plans, FDA, March 2005 (http://www.fda.gov/)

Risk management (CIOMS IV)
The making of decisions concerning risks, or action to reduce the consequences or probability of occurrence.
Adopted from: Risk: Analysis, Perception and Management. Report of a Royal Society Study Group. The Royal Society. London, 1992.

189. **Risk management plan (RMP)** (CIOMS DILI)
(In the European Community) A detailed description of the risk management system [Directive 2001/83/EC Art 1(28c)].
The risk management plan established by the marketing authorisation holder shall contain the following elements: (a) an identification or characterisation of the safety profile of the medicinal product(s) concerned; (b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned; (c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) a documentation of post-authorisation obligations that have been imposed as a condition of the marketing authorisation [Implementing Regulation 520/2012 Art 30(1)].[15]
Modified from: CIOMS Working Group IX.

(Note: The CIOMS IX report reflects the definition given in Revision 3 of the EU GVP document, whereas the above entry reflects that in EU GVP Revision 4.)

Risk management plan (RMP) (CIOMS IX)
A detailed description of the risk management system [Directive 2001/83/EC Art 1(28c)]. To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterize further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

190. **Risk management system** (CIOMS IX)
A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [Directive 2001/83/EC Art 1(28b)].
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

Risk management system (CIOMS VIII, also available in Chinese)
A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risk relating to medicinal products, and the assessment of the effectiveness of those interventions.
Adopted from: Guideline on Risk Management Systems for medicinal products for human use, Volume 9A of Eudralex, Chapter I.3, March, 2007.

191. **Risk minimization** (CIOMS DILI)
In a broader sense the term risk minimisation is used as an umbrella term for prevention or reduction of the frequency of occurrence of an undesirable outcome (see risk prevention) and reduction of its severity should it occur (see risk mitigation).
Adopted from: CIOMS Working Group IX.

Risk minimization (CIOMS IX)
In a broader sense the term risk minimisation is used as an umbrella term for prevention or reduction of the frequency of occurrence of an undesirable outcome (see risk prevention) and reduction of its severity should it occur (see risk mitigation).
Proposed by CIOMS Working Group IX.

192. **Risk minimisation action plans (RiskMAPs)** (CIOMS IX)
FDA approved strategic safety programme designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting. Prior to REMS being introduced through the Food and Drug Administration Amendments Act of 2007, in

2005, FDA had issued a guidance for industry on Development and use of risk minimisation action plans (the RiskMAP guidance), that described how to develop RiskMAPs, select tools to minimise risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.

Modified from: FDA Draft Guidance for Industry 'Format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications'.

{The web link given in the CIOMS IX Working Group report redirects to an updated version of the guidance (October 2017) found here.}

193. **Risk minimisation-burden balance** (CIOMS IX)
A measure of the effectiveness of risk minimisation relative to the burden it imposes. (See Effectiveness of risk minimisation and Burden).

Proposed by CIOMS Working Group IX.

194. **Risk minimisation exposure** (CIOMS IX)
One of several measures of the fidelity of implementing a risk minimisation intervention. It describes the amount of risk minimisation delivered to the risk minimisation target (*e.g.* healthcare professional, patient) in terms of content, frequency and duration of an intervention.

Modified from: Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation Science 2007, 2:40 available at this webpage, accessed 19 January 2014.

195. **Risk minimisation intervention / Risk minimisation activity / Risk minimisation measure (synonyms)** (CIOMS IX)
Application of one or more risk minimisation tools with the intent to reduce the frequency of occurrence of an undesirable outcome or to reduce its severity should it occur.

Proposed by CIOMS Working Group IX.

196. **Risk minimisation plan** (CIOMS IX)
Part of the risk management plan which details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. It includes both routine and additional risk minimisation activities.

Modified from: Eudralex, Volume 9a, of the Rules governing medicinal products in the European Union. Guidelines on pharmacovigilance for medicinal products for human use. Final, September 2008: 1.3.

197. **Risk minimisation programme** (CIOMS IX)
A system of risk minimisation action(s) that are described and derived from a risk minimisation plan.

Proposed by CIOMS Working Group IX.

198. **Risk minimisation strategy** (CIOMS IX)
Direction and scope of planned risk minimisation as specified by objective(s) and target(s) to reach defined goal(s).

Proposed by CIOMS Working Group IX.

199. **Risk minimisation target** (CIOMS IX)
Recipient or audience for a risk minimisation intervention instrumental to its implementation, *e.g.* healthcare providers.
Proposed by CIOMS Working Group IX.

200. **Risk minimisation tool** (CIOMS IX)
A risk minimisation tool is a method for delivering an intervention intended to minimise specific/specified risks.
Modified from: FDA Guidance for Industry Development and Use of Risk Minimization Action Plans, March 2005.

201. **Risk mitigation** (CIOMS DILI)
Reduction of the severity of an undesirable outcome should it occur.
Adopted from: CIOMS Working Group IX.

Risk mitigation (CIOMS IX)
Reduction of the severity of an undesirable outcome should it occur.
Proposed by CIOMS Working Group IX.

202. **Risk prevention** (CIOMS DILI)
Reduction of the frequency of occurrence of an undesirable outcome in a population, population subset or an individual patient.
Adopted from: CIOMS Working Group IX.

Risk prevention (CIOMS IX)
Reduction of the frequency of occurrence of an undesirable outcome in a population, population subset or an individual patient.
Proposed by CIOMS Working Group IX.

203. **Risk ratio** (CIOMS X)
The ratio of one proportion to another. The way that it is commonly estimated from sample data is illustrated in Annex II. Glossary case study.
Proposed by CIOMS Working Group X.

204. **Risks related to use of a medicinal product** (CIOMS IX)
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [Directive 2001/83/EC Art 1(28)].
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

205. **Routine pharmacovigilance** (CIOMS IX)
Set of activities required by applicable regulations as a minimum standard of pharmacovigilance to be conducted for all medicinal products.
Proposed by CIOMS Working Group IX.

206. **Routine risk minimisation activities** (CIOMS IX)
Risk minimisation activities that apply to all medicinal products and relate to standard activities such as product labelling, limitations on drug pack size and the legal status of the product (*e.g.*, drug scheduling).
Modified from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

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207. **Safety concern** (CIOMS IX)
An important identified risk, important potential risk or missing information.
Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

208. **Safety-related outcome of interest**, see also Outcome indicators (CIOMS IX)
Clinical outcome indicator closely linked to the goal(s) of a risk minimisation programme which has been selected as suitable indicator of relevance for measuring its effectiveness.
Proposed by CIOMS Working Group IX.

209. **Scatterplots** (CIOMS VI)
Graphical diagrams that show the variation of individual continuous values for two variables in a set of data. Different symbols can be used for the points themselves to distinguish between different groups. They are often used to show before and after treatment values of the same variable (*e.g.*, the liver enzyme value for each patient plotted as a function of time).
Proposed by CIOMS Working Group VI.

210. **Sensitivity** (CIOMS DILI)
The proportion of people with a positive test result among those with the target condition.
Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

Sensitivity (CIOMS VI)
This can have two meanings in statistical terms. The first is whether an analysis has high power (sensitive) or not. It can also mean sensitivity to the assumptions made for an analysis, *i.e.*, a test of whether the results of the analysis change when assumptions about effects (parameters) are changed.
Proposed by CIOMS Working Group VI.

211. **Sensitivity analysis** (CIOMS X)
An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.
Adopted from: Glossary of Terms in the Cochrane Collaboration. Available from this webpage.

212. **Sequential meta-analysis** (CIOMS X)
A particular form of a cumulative meta-analysis accounting for multiple testing in which clinical trials can be stopped early (or planned future trials could be stopped before they start) based on interim analyses or sequential analyses. In principle, sequential analyses can also be used to decide whether enough evidence has been gathered in completed trials to make further trials unnecessary.
Proposed by CIOMS Working Group X.

213. **Serious** (CIOMS IV)
Usually the word ‘‘serious’’ has two connotations. One is the common use of the term ‘‘medically serious,’’ implying a diagnosis or condition that is dangerous, critical or alarming. The other is a regulatory-administrative definition created for purposes of defining regulatory reporting obligations for adverse reaction reports. Although different regulators use several similar definitions, the following definition encompasses all of them and is the official definition given in the 1995 Guideline on expedited reporting of adverse drug reactions, of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [Footnote 5]:

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

– results in death;
– is life-threatening;
– requires inpatient hospitalization or prolongation of hospitalization;
– results in persistent or significant disability/incapacity;
– is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

[Footnote 5 in the report:] Gordon, A.J. Implementation and Impact of ICH Guideline E2A: Definitions and Standards for Expedited Reporting. Proceedings of the Third International Conference on Harmonization, Queens University, Belfast, pp. 461-469, 1996.

Proposed by CIOMS Working Group IV.

Serious (CIOMS II)
Fatal, life-threatening, involved or prolonged inpatient hospitalization, or resulted in persistent or significant disability or incapacity. These are the four categories specified on the “CIOMS Form” designed by the CIOMS Working Group for reporting of serious adverse drug reactions (CIOMS Working Group I). CIOMS safety updates require consideration of all drug interactions, cases of

drug abuse, and cases of significant overdosage; therefore these cases could also be considered "serious" and included in line listings in CIOMS safety up-dates or added as a separate table.

Proposed by CIOMS Working Group II.

214. **Serious adverse event** (CIOMS IX)

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Adopted from: Article 2(o) of Directive 2001/20/EC.

→ See also Serious adverse event following immunization (AEFI) (TERMS AND DEFINITIONS — VACCINES)

215. **Serious adverse reaction**, see also Adverse reaction (CIOMS IX)

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [Directive 2001/83/EC Art 1(12)].

Adopted from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

{Unchanged in the Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

Serious adverse reaction/Adverse drug reaction (CIOMS VIII, also available in Chinese)

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Note: Medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above, should also usually be considered serious. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Modified from: Definitions and Standards for Expedited Reporting, ICH Harmonised Tripartite Guideline, E2A, Current Step 4 version, dated 27 October 2004.

Serious adverse event or reaction (CIOMS VII)

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious as well. Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

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

Adopted from: ICH Guideline E2A: Definitions and Standards for Expedited Reporting and ICH Guideline E2D: Post-approval Safety Data Management – Note for Guidance on Definitions and Standards for Expedited Reporting.

In the EU Directive 2001/20/EC on Clinical trials: "Serious Adverse Event or Serious Adverse Reaction" – any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Commentary: The ICH definition of a serious adverse event (AE) or adverse drug reaction (ADR) has been adopted for post marketing applications in ICH Guideline E2D. The EU definition given above is considered by the CIOMS Working Group as incomplete without the paragraph beginning with "Medical and scientific judgement…" in the ICH definition.

Serious adverse event or reaction: standard criteria (CIOMS VI)

Any untoward medical occurrence that at any dose

- Results in death,
- Is life-threatening,*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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* Note: the term "life-threatening" refers to an event or reaction in which the patient was at risk of death at the time of the event or reaction; it does not refer to an event or reaction which hypothetically might have caused death if it were more severe.

Adopted from: ICH Guideline E2A: Definitions and Standards for Expedited Reporting

In the EU: "Serious Adverse Event or Serious Adverse Reaction" – any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Commentary: The ICH definition of a serious adverse event (AE) or adverse drug reaction (ADR) has been adopted for postmarketing applications in ICH Guideline E2D. The EU definition given above is considered by the CIOMS Working Group as incomplete without the paragraph beginning with "Medical and scientific judgment …." in the ICH definition.

216. **Severe/Severity** (CIOMS IV)

The term severe is not synonymous with serious in this context. Severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction).

Proposed by CIOMS Working Group IV.

217. **Signal** (CIOMS VIII, also available in Chinese)
Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Modified from: Hauben M, Aronson J.K. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Safety, 2009, 32:1-12.

→ See also Signal (TERMS AND DEFINITIONS — VACCINES)

Signal (CIOMS DILI)
Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial.

Modified from CIOMS Working Group VIII.

{The CIOMS VIII definition should be considered as the current one. It corresponds to the definition in the EMA GVP Annex 1 Rev. 4. The last clause was omitted from the above definition inadvertently, not as a result of a consensus by the DILI WG.}

Signal (CIOMS VII)
A report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance.

Adopted from: Benefit-Risk Balance for Marketed Drugs. Report of CIOMS Working Group IV, CIOMS, Geneva, 1998; and Dictionary of Pharmacoepidemiology, by B. Bégaud, John Wiley & Sons, Ltd., Hoboken, USA, 2000

Commentary: A signal can arise from non-clinical as well as clinical sources. It should be based on data and not theory, and can refer not only to a new (unexpected) and potentially important event, but also to an unexpected finding for an already known event, such as information on an adverse drug reaction (ADR) related to the nature (specificity), intensity, rate of occurrence or other clinically relevant finding that represents a meaningful change from that expected in the subject/patient population under investigation or treatment. A signal is not a con- firmed finding, but is generally referred to as an hypothesis- generating situation that must be validated ("signal strengthening") or disproved.

An older definition of a signal by the WHO Collaborating Centre for International Drug Monitoring (BMJ, 304:465, 22 February 1992) focused on post-marketing conditions and predated the new definitions of adverse event and adverse reaction introduced under ICH: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information."

Signal (CIOMS VI)
A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance.

Combined and modified from:
Report of CIOMS Working Group IV.
Dictionary of Pharmacoepidemiology, by B. Begaud, John Wiley & Sons, 2000.

Commentary: A signal can arise from non-clinical as well as clinical sources. It should be based on data and not theory, and can refer not only to a new (unexpected) and potentially important event, but also to an unexpected finding for an already known event, such as information on an ADR related to the nature (specificity), intensity, rate of occurrence or other clinically relevant finding that represents a meaningful change from that expected in the subject/patient population under investigation or treatment. A signal is not a confirmed finding but is generally referred to as a hypothesis-generating situation that must be validated ("signal strengthening") or disproved.

An older definition of a signal by the WHO Collaborating Centre for International Drug Monitoring (British Medical Journal, 304:465, 22 February 1992) focused on post-marketing conditions and predated the new definitions of adverse event and adverse reaction introduced under ICH: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information."

Signal (CIOMS IV)
A report (or reports) of an event that may have a causal relationship to one or more drugs; it alerts health professionals and should be explored further [Footnote 6].

Note: In addition to information on a new (unexpected), potentially important event, a signal can refer to an unexpected finding, or a finding exceeding a determined threshold, for an already known event—for example, data involving the nature (specificity), intensity or rate of occurrence.

Adopted from the reference cited in Footnote 6, see below.

[Footnote 6 in the report] Hartzema, A.G., Porta, M.S. and Tilson, H.H. Pharmacoepidemiology: An Introduction. Harvey, Whitney Books. Cincinnati, Ohio, 1988.

218. **Signal detection** (CIOMS IX)
The act of looking for and/or identifying signals using event data from any source.

Adopted from: CIOMS Working Group VIII.

Signal detection (CIOMS VIII, also available in Chinese)
The act of looking for and/or identifying signals using event data from any source.

Proposed by CIOMS Working Group VIII.

219. **Signal management** (CIOMS VIII, also available in Chinese)
A set of activities including signal detection, prioritization and evaluation to determine whether a signal represents a risk which may warrant further assessment, communication or other risk minimization actions in accordance with the medical importance of the issue.

Proposed by CIOMS Working Group VIII.

220. **Signal, verified** (CIOMS VIII, also available in Chinese)
A signal of suspected causality that has been verified either by its nature or source, *e.g.* a definitive anecdote or a convincing association that has arisen from a randomized clinical trial or by formal verification studies.

Modified from: Hauben M, Aronson J.K. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Safety, 2009, 32:1-12.

221. **Significance, Significant, Significantly** (CIOMS VI)
These terms refer to the quantitative interpretation of statistical tests. These tests produce levels of probabilities (P-values) that indicate whether the differences measured are low (significant) or high (non-significant) if there are no true differences. The conventional cut-off for "significant" is usually P=0.05 (5%), but reliance only on P values or "significance" can be misleading. Adverse reactions are often rare so that power is low and statistically significant results may not be seen even in the presence of clinically important effects.

Proposed by CIOMS Working Group VI.

222. **Simes** (CIOMS VI)
A method similar to a Bonferroni correction (see above) but with greater power.
Proposed by CIOMS Working Group VI.

223. **Specificity** (CIOMS DILI)
The proportion of people who are truly free of a designated disorder who are so identified by the test. The test may consist of, or include, clinical observations.
Adopted from: JAMAevidence® Glossary. (Webpage, accessed 29 March 2020)

224. **Sponsor** (CIOMS DILI)
An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial.
Adopted from: CIOMS Working Group IX.

Sponsor (CIOMS IX)
An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial [Directive 2001/20/EC Art 2(e)].
Adopted from: Eudralex Volume 9a (Sep 08), Glossary 1.3.

Sponsor (CIOMS VII)
An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
Adopted from: ICH Guideline for Good Clinical Practice E6(R1).

Sponsor (CIOMS VI)
An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Adopted from: ICH Guideline: E6 Good Clinical Practice
In the EU: Identical to the above definition.

225. **Spontaneous report** (CIOMS VIII, also available in Chinese)
An unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization that describes one or more suspected adverse drug reactions in a patient who was given one or more medicinal products.
Modified from Pharmacovigilance Planning, ICH Harmonised Tripartite Guideline, E2E, Current Step 4 version, dated 18 November 2004.

226. **Standard of care** (CIOMS IX)
Diagnostics and/or treatment provided by healthcare professionals that are based on scientifically accepted evidence and comply with common current professional practice in given circumstances.
Proposed by CIOMS Working Group IX.

227. **Statistic of disproportionate reporting (SDR)** (CIOMS VIII, also available in Chinese)
A numerical result above a preset threshold generated from any data mining algorithm using disproportionality analysis applied to a spontaneous report database. An SDR alerts medical assessors to a specific adverse event reported for a particular medicinal product (drug-event pair) that should be explored further.

Note: SDRs that originate from spontaneous report databases cannot be interpreted as scientific evidence for establishing causality between medicinal products and adverse events, and thus they are distinct from statistical associations that originate from formal epidemiological studies.

Modified from: Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system. London, Doc. Ref. EMEA/106464/ 2006 rev. 1.

228. **Structural alerts** (CIOMS DILI)
In order to identify compounds with potential toxicity problems, particular attention is paid to structural alerts, which are high chemical reactivity molecular fragments or fragments that can be transformed via bioactivation by human enzymes into fragments with high chemical reactivity. The concept has been introduced in order to reduce the likelihood that future candidate substances as pharmaceuticals will have undesirable toxic effects.

Adopted from: Limban C, Nuţă DC, Chiriţă C, Negreș S, Arsene AL, Goumenou M, et al. The use of structural alerts to avoid the toxicity of pharmaceuticals. Toxicol Rep. 2018;5:943-53. (PMC full text)

229. **Summary-level data** (CIOMS X)
Refers to summary statistics (*e.g.* mean, standard deviation) at the level of a group of participants (*e.g.* treatment and control group) in a single study.

Proposed by CIOMS Working Group X.

230. **Summary of product characteristics (SmPC)** (CIOMS IX)
{Also known as SPC}

Part of the marketing authorisation of a medicinal product in the EU setting out the agreed position of the product as distilled during the course of the assessment. It is the basis of information for healthcare professionals on how to use the product safely and effectively.

Modified from: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

{Included in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

{In the EU GVP Annex I (Rev 4, October 2017), the text has changed to this: "Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process which includes the information described in Article 11 of Directive 2001/83/EC. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics (based on A Guideline on Summary of Product Characteristics, Volume 2C of the Rules Governing Medicinal Products in the EU Rev 2)."}

231. **Survival analysis** (CIOMS VI)
A statistical analytical technique originally developed for studying time until death (survival time) following an intervention (or no intervention), such as in cancer treatment trials. However, it is applicable to studying time to some other type of event such as an adverse reaction or a non-fatal myocardial infarction. Some types of survival analyses use non-parametric tests such as the Log Rank Test, others can be "semi-parametric" such as the Cox model (see above), or parametric (exponential or Weibull (see below)).

Proposed by CIOMS Working Group VI.

232. **Surrogate endpoint** (CIOMS VI)

A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit or harm or lack of benefit or harm, *e.g.* a biomarker. A surrogate endpoint is expected to predict clinical outcome based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence and may be used as a primary endpoint when appropriate.

Combined from:
ICH Harmonised Tripartite Guideline - General considerations for clinical trials E8 (Jul 1997).
Biomarkers definitions working group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001, 69: 89–95.

233. **Survey** (CIOMS IX)

Patient or healthcare professional surveys are designed to gather information to assess a safety signal, knowledge about a labeled adverse event, use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist, or confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names. A written protocol should include objectives for the survey and a detailed description of the research methods.

Modified from: FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005, March.

234. **Suspected unexpected serious adverse reactions (SUSAR)** (CIOMS VII)

This term and acronym come from an EU Clinical trial Directive Guidance on expedited reporting: "All suspected adverse reactions related to an IMP (the tested IMP and comparators) which occur in the concerned trial that are both unexpected and serious (SUSARs) are subject to expedited reporting."

[Note: IMP = investigational medicinal product]

Adopted from: EU Directive 2001/20/EC on Clinical Trials (Article 17). Detailed guidance on the collection, verification and presentation of adverse reports arising from clinical trials on medicinal products for human use, April 2006. ENTR/CT 3 Revision 2.

See also, Detailed guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module. ENTR/CT 4. Revision 1).

Suspected unexpected serious adverse reaction (SUSAR) (CIOMS VI)

This term and acronym were introduced within one of the guidances to the EU Clinical Trial Directive in connection with expedited reporting: "All suspected adverse reactions related to an IMP (the tested IMP and comparators) which occur in the concerned trial that are both unexpected and serious (SUSARs) are subject to expedited reporting."

[Note: IMP = investigational medicinal product]

Adopted from: European Commission. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2004.

{Note: The above-mentioned guidance has since been revised. }

235. **Systematic error** (CIOMS VI)
An error that is not random/haphazard, but which will occur in the same direction within one or many studies. For example, studying treatments for too short a duration will systematically underestimate long-term effects.
Proposed by CIOMS Working Group VI.

236. **Systematic review** (CIOMS X)
A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies.
Adopted from: Glossary of Terms in The Cochrane Collaboration. Available from this webpage.

T

237. **Target population** (CIOMS IX)
While generally referring to the patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information or specifically to populations as defined in epidemiologic studies, in the context of risk minimisation in this book target population refers to the patients targeted by a risk minimisation activity which may be a subset of or overlap with the former.
Modified from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).
{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 (Rev 4, October 2017).}

238. **Targeted follow-up questionnaire** (CIOMS IX)
A questionnaire used to capture specific follow-up/further information from a reporter for an adverse event of special interest. It is part of routine pharmacovigilance.
Proposed by CIOMS Working Group IX.

239. **Targeted medical event (TME)** (CIOMS VIII, also available in Chinese)
An adverse event of special interest for a particular medicinal product.
Modified from: Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system. London, Doc. Ref. EMEA/106464/ 2006 rev. 1 (Webpage, accessed December 2020)

240. **Trial** (CIOMS X)
An experiment in which two or more interventions, one of which could be a control intervention or "usual care", are compared by being randomly allocated to participants. In most trials, one intervention is assigned to each individual but sometimes assignment is to specific groups of individuals (*e.g.* in a household) or interventions are assigned within individuals (*e.g.* in different orders or to different parts of the body).
Proposed by CIOMS Working Group X.

241. **Tumour-agnostic therapy** (CIOMS DILI)
A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumour-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy. Also called tissue-agnostic therapy.
Adopted from: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage)

242. **Type I and Type II errors** (CIOMS VI)
A Type I error in statistical testing is a false positive (see above). A Type II error is a false negative (see above), usually arising by studying too few individuals.
Proposed by: CIOMS Working Group VI.

V – W – Y

243. **Validation** (CIOMS DILI)
A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose.
Adopted from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (Internet). Silver Spring (MD): U.S. Food and Drug Administration; 2016-20. Co-published by U.S. National Institutes of Health, Bethesda (MD). Published on January 28, 2016, last update: 2 May 2018. (Webpage)

244. **Weibull distribution** (CIOMS VI)
A distribution of data that is relevant to parametric survival analyses.
Proposed by CIOMS Working Group VI.

245. **Weight** (CIOMS X)
The weight of an individual study estimate of treatment effect is the relative amount that the study-specific estimate contributes to the estimation of the overall treatment effect. The weights in a fixed-effect model are often determined by the inverse of the within-study variance and in a random-effects model by the inverse of the within-study plus among-study variance. However, there is no necessary connection between the weights of the individual study estimates and fixed-effect or random-effects models. The choice of weights can be informed by other considerations.
Proposed by CIOMS Working Group X.

246. **Yate's correction** (CIOMS VI)
A correction applied to data in a 2 x 2 contingency table when carrying out a chi-square test. With modern computer software, however, a Fisher's exact test is generally preferred.
Proposed by CIOMS Working Group VI.

TERMS AND DEFINITIONS — VACCINES

A – B – C – D

1. **Absolute risk** (CIOMS WG on Vaccine Safety – AVSS)
Probability that a specified event will occur in a specified population, in contrast to the relative risk of the event.
Adopted from: http://medical-dictionary.thefreedictionary.com/absolute+risk, accessed 5 May 2021

→ Back to Absolute risk (TERMS AND DEFINITIONS — GENERAL)

2. **Active vaccine safety surveillance** (CIOMS WG on Vaccine Safety – AVSS)
A data collection system that seeks to ascertain as completely as possible the number of adverse events following immunization (AEFIs) in a given population via a continuous organized process.
Proposed by CIOMS Working Group on Vaccine Safety.

→ Back to Active surveillance (TERMS AND DEFINITIONS — GENERAL)

3. **Adverse event following immunization (AEFI)** (CIOMS WG on Vaccine Safety – AVSS)
Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Adopted from: CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012.
{See also the cause-specific definitions of an Adverse event following Immunization (AEFI): Vaccine product-related reaction; Vaccine quality defect-related reaction, Immunization error-related reaction, Immunization anxiety-related reaction and Coincidental event.}

→ Back to Adverse event (TERMS AND DEFINITIONS — GENERAL)

Adverse event following immunization[1] (AEFI) (CIOMS/WHO WG on Vaccine Pharmacovigilance)
Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

[Footnote [1] in the report:] "Immunization" as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, *i.e.* handling, prescribing and administration of the vaccine.
Proposed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

4. **Aggregate data** (CIOMS WG on Vaccine Safety – AVSS)

In statistics, aggregate data describes data combined from several measurements.
When data are aggregated, groups of observations are replaced with summary statistics based on those observations.

Adopted from: Aggregation and Restructuring of data (chapter 5.6 from the book "R in Action", Manning Publications)

5. **Background rates** (CIOMS WG on Vaccine Safety – AVSS)

Rate of an event (occurring/reported/measured) due to all cases fitting the case definition, which are expected to occur in the community in the absence of the putative vaccine.

Adopted from:. Guide to the WHO information sheets on observed rates of vaccine reactions. Geneva: World Health Organization;12 April 2012. (PDF, accessed 5 May 2021)

6. **Clinical vaccine failure** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

{See also Immunological vaccine failure}

Confirmed clinical vaccine failure

The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.

The application of this definition requires clinical and laboratory confirmation (or epidemiological link to a confirmed case, where applicable) that the actual disease is vaccine preventable, *i.e.* that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine.

● Example (consistent with clinical vaccine failure): Report of a 60-year-old patient who received one dose of 23-valent pneumococcal polysaccharide vaccine and who is diagnosed with bacteraemic pneumonia with *S. pneumoniae* Type 19F six months later. In this case the patient was appropriately immunized, and he got sick at a time when he should have mounted an immunologic response to the vaccine. In addition, his exposure would have been at a time that protection could have been expected as the incubation period for pneumococcal disease is probably days to perhaps weeks.

● Example (inconsistent with clinical vaccine failure): Report of a 23-year-old patient, recently vaccinated with hepatitis B vaccine on a schedule of 0, 1, and 6 months. The patient developed jaundice and fever two weeks after the last dose and was found to be antiHBc-IgM* and HBsAg* positive. In this case, although the patient was appropriately immunized, his exposure to the hepatitis B virus must have occurred prior to the complete vaccination series based on the incubation of the infection (2-6 months). Because protection would not be expected to have been reliably achieved prior to exposure or infection this would *not* be considered a vaccine failure.

**{antiHBc: Hepatitis B core antibody; IgM: Immunoglobulin M; HBsAG: Hepatitis B surface antigen}*

Suspected clinical vaccine failure

Suspected vaccine failure is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, *e.g.* invasive pneumococcal disease of unknown serotype in a fully vaccinated person. Applying this definition also requires that the incubation period and the normal delay for the protection to be acquired as a result of immunization have been taken into account.

● Example (consistent with suspected clinical vaccine failure): A 2-year-old boy received four doses of *Haemophilus influenzae* type B conjugate vaccine at 2, 4, 6 and 12 months of age. He develops bacteraemia with *H. influenzae*, but no serotyping is performed on the organism. In this case the patient is fully and appropriately immunized and the exposure should have occurred at a time when protection would be expected based on incubation and time to response. However, it is not clear that the disease was caused by *H. influenzae* type B, i.e. that it would have been preventable by the vaccine.

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

7. **Coincidental event** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

{This is one of five cause-specific definitions of an Adverse event following immunization (AEFI). The other four are: Vaccine product-related reaction; Vaccine quality defect-related reaction, Immunization error-related reaction and Immunization anxiety-related reaction.}

An adverse event following immunization (AEFI) that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

8. **Common technical document** (CIOMS WG on Vaccine Safety – AVSS)

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of medicines to the regulatory authorities in the three regions of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It is an internationally agreed format for the preparation of applications regarding new medicines intended to be submitted to regulatory authorities in participating countries.

Source: Adapted by CIOMS Working Group on Vaccine Safety from ICH, Wikipedia, and FDA definitions.

{See the ICH M4 Step 4 Guideline of 15 June 2016 and the U.S. FDA Guidance for Industry M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use, October 2017.}

I – K – P

9. **Immunization and vaccination** (CIOMS WG on Vaccine Safety – VSC)

"Immunization" as used in this report means the usage of a vaccine for the purpose of immunizing individuals. It is generally acknowledged that (1) "immunization" is a broader term than "vaccination", including active and passive immunization, and (2) immunization when used strictly implies an immune response. In keeping with other key published literature in the field of immunization, the terms "immunization" and "vaccination" are generally used interchangeably in the current report.

Adopted from: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Immunization and vaccination (CIOMS/WHO WG on Vaccine Pharmacovigilance)

"Immunization" as used in this report means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/packaging site, *i.e.* handling, prescribing and administration of the vaccine.

It is generally acknowledged that (1) "immunization" is a broader term than "vaccination", including active and passive immunization, and (2) immunization when used strictly implies an immune response. In keeping with other key published literature in the field of immunization, the terms "immunization" and "vaccination" are – in general – used interchangeably in the current report. For consistency, a few specific phrases where either term was considered to be implicit or in common use have been maintained (*e.g.*, "immunization programme", "mass vaccination campaign").

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

10. **Immunization anxiety-related reaction** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

{This is one of five cause-specific definitions of an Adverse event following immunization (AEFI). The other four are: Vaccine product-related reaction; Vaccine quality defect-related reaction, Immunization error-related reaction and Coincidental event.}

An adverse event following immunization (AEFI) arising from anxiety about the immunization.

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Evolving definition

{This definition is evolving. Find a summary of the current WHO concept here: McMurtry CM. Managing immunization stress-related response: A contributor to sustaining trust in vaccines. Can Commun Dis Rep. 2020 Jun 4;46(6):210-218. (PMC full text)}

11. **Immunization error-related reaction** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

{This is one of five cause-specific definitions of an Adverse event following immunization (AEFI). The other four are: Vaccine product-related reaction; Vaccine quality defect-related reaction, Immunization anxiety-related reaction and Coincidental event.}

An adverse event following immunization (AEFI) that is caused by inappropriate [Footnote 2] vaccine handling, prescribing or administration and thus by its nature is preventable.

[Footnote 2 in the report:] "Inappropriate" refers to usage (handling, prescribing and administration) other than what is licensed and recommended in a given jurisdiction based on scientific evidence or expert recommendations.

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

12. **Immunological vaccine failure** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

{See also Clinical vaccine failure}

Confirmed immunological vaccine failure

In addition to clinical vaccine failure, there is the possibility of immunological vaccine failure, not necessarily associated with a clinical manifestation of the vaccine-preventable disease. Immunological failure is defined as failure of the vaccinee to develop the accepted marker of protective immune response after being fully and appropriately vaccinated. This definition requires that there is an accepted correlate or marker for protection, and that the vaccinee has been tested or examined at an appropriate time interval after completion of immunization.

- Example (consistent with immunological vaccine failure): A 32-year old health-care worker received three doses of hepatitis B vaccine on a schedule of 0, 1 and 6 months and anti-HBs antibody testing of her serum six weeks after the third dose revealed a value of <10 U/l. This health-care worker was considered an immunological failure of hepatitis B vaccination.

Suspected immunological vaccine failure

- Example (inconsistent with immunological vaccine failure): Same situation as above apart from anti-HBs antibody testing being done only eight years after the third dose with a value of <10 U/l. Since the time interval of antibody testing was inappropriate, immunological failure is possible but was not confirmed as such.

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

13. **Knowledge gap** (CIOMS WG on Vaccine Safety – AVSS)

Refers to lack of available or easily accessible information on vaccines in countries which need the respective information in contexts like vaccine introduction, new safety issue, change in the nature of the vaccination program, or which have an inadequate passive surveillance system. This lack of information equals a research gap or question which has not been answered sufficiently.

Proposed by the CIOMS Working Group on Vaccine Safety.

14. **Passive vaccine safety surveillance** (CIOMS WG on Vaccine Safety – AVSS)
The spontaneous reporting of adverse events following immunization (AEFI) by immunization service providers, hospitals, and patients to the administrative level appropriate in each country depending on its national surveillance system. From there, reports are sent to the next reporting level(s), ending at the international institutions responsible for global AEFI surveillance.

Modified for this context from: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF, accessed 5 May 2021)

→ Back to Passive surveillance (TERMS AND DEFINITIONS — GENERAL)

S

15. **Serious adverse event following immunization (AEFI)** (CIOMS WG on Vaccine Safety – AVSS)
Adverse event following immunization (AEFI) that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly/ birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.

Adopted from: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF, accessed 5 May 2021)

→ Back to Serious adverse event (TERMS AND DEFINITIONS — GENERAL)

Serious adverse event (CIOMS/WHO WG on Vaccine Pharmacovigilance)
This concept is defined by ICH in the ICH E2A and E2D guidelines [References 24, 25]. Seriousness is based on patient/event outcome or action criteria and defines regulatory reporting obligations. An adverse event following immunization (AEFI) will be considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The ICH E2A and E2D guidelines also state that other situations, such as other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above, should also be considered serious after applying medical and scientific judgment. Those "other situations" are open to interpretation and could vary from jurisdiction to jurisdiction. It is important to note that 'serious' and 'severe' are often used as interchangeable terms but they are not. Severe is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance.

The criteria for seriousness have been discussed in the CIOMS V report on Current Challenges in Pharmacovigilance. The application of the criteria is dependent on their interpretation and health practices in a particular setting. For example, variability in hospital admission practices may result in observed differences in the proportion of reported serious and non-serious events in different settings and databases.

[Reference 24 in the report:] Clinical safety data management: definitions and standards for expedited reporting. E2A. ICH, 1994. (PDF, accessed 17 May 2021)

[Reference 25 in the report:] Post-approval safety data management: definitions and standards for expedited reporting. E2D. ICH, 2003. (PDF, accessed 17 May 2021)

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance

16. **Signal** (CIOMS/WHO WG on Vaccine Pharmacovigilance)
Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Adopted from: CIOMS Working Group VIII.

Points to consider regarding differences between vaccines and drugs in signal detection:

At its October 2007 meeting, this Working Group took note of the work being undertaken by the CIOMS Working Group VIII on Signal Detection and determined that there was no need to develop a separate definition of "signal" for vaccine pharmacovigilance. Rather, the Working Group requested that key considerations for vaccine signal detection be prepared for inclusion in the CIOMS VIII report. The final report by this Working Group on the points to consider for vaccine signal detection was endorsed in April 2008 and submitted for inclusion as an annex in the Report of the CIOMS Working Group VIII on Signal Detection (1). Editorial changes to those points have been included in this report (see section 3.4). Further, the definition of a signal by the CIOMS Working Group VIII is hereby adopted for this report (see Glossary and section 3.4).

→ Back to Signal (TERMS AND DEFINITIONS — GENERAL)

17. **Significant knowledge gap** (CIOMS WG on Vaccine Safety – AVSS)
{See also Knowledge gap}
If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a significant knowledge gap (SKG).

Proposed by: CIOMS Working Group on Vaccine Safety.

18. **Surveillance** (CIOMS WG on Vaccine Safety – AVSS)
The continuing, systematic collection of data that are analysed and disseminated to enable decision- making and action to protect the health of populations.

Adopted from: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF, accessed 5 May 2021)

V

19. **Vaccine approval, authorization or licensure** (CIOMS WG on Vaccine Safety – VSC)
The terms "approval", "authorization" and "licensure" in the context of vaccine (and drug) regulation in different jurisdictions mean the declaration by a regulatory authority that a product following review was found to have a positive benefit-risk profile and is approved for marketing and use. For consistency we have adopted "licensure" to cover any of these regulatory procedures or declarations. "Marketing" (or "post-marketing", etc.) is usually used to describe the phase of vaccine distribution following the manufacturer's decision to market the vaccine. The manufacturer may decide not to market a product even though licensure has been granted by the regulatory authority. While "marketing" differs in meaning, we have adopted, for consistency, the terms "pre-licensure" and "post-licensure" throughout this report to include everything that follows licensing of the product (*i.e.* "post-licensure" includes post-marketing considerations that would apply in the specific context in which the term is used)

Adopted from: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Vaccine approval, authorization or licensure (CIOMS/WHO WG on Vaccine Pharmacovigilance)
The terms "approval", "authorization" and "licensure" in the context of vaccine (and drug) regulation in different jurisdictions mean the declaration by a regulatory authority that a product following review was found to have a positive risk/benefit and the product is approved for marketing and use. For consistency, we have adopted "licensure" to cover any of these regulatory procedures or declarations. "Marketing" (or "post-marketing", etc.) is usually used to describe the phase of vaccine distribution following the manufacturer's decision to market the vaccine. The manufacturer may decide not to market a product even though licensure has been granted by the regulatory authority. While "marketing" differs in meaning we have adopted, for consistency, the term "post-licensure" throughout this report to include everything that follows licensing of the product (*i.e.*, "post-licensure" includes post-marketing considerations that would apply in the specific context in which the term is used).

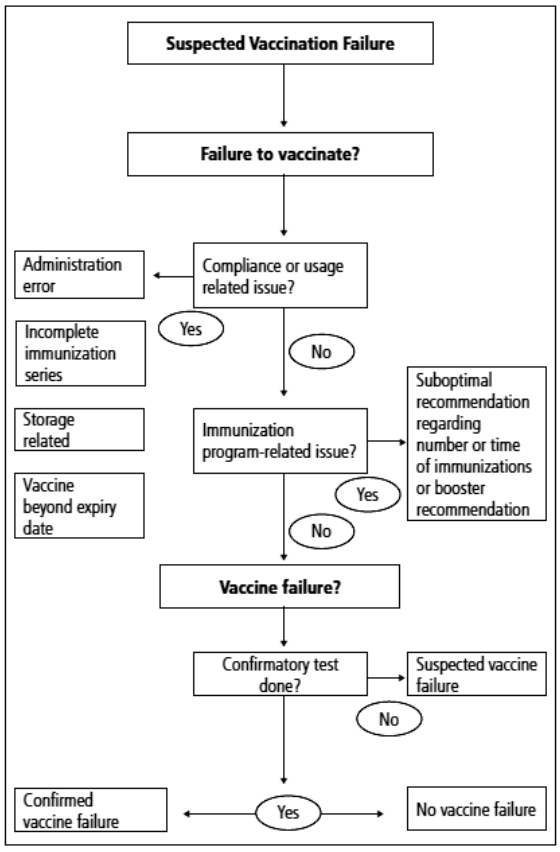
Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

20. **Vaccination failure** (CIOMS/WHO WG on Vaccine Pharmacovigilance)
{See also Vaccine failure}

Vaccination failure may be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist [22, 23]. Primary failure (for example, lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity).

Vaccination failure can be due to 1) vaccine failure or 2) failure to vaccinate, *i.e.* that an indicated vaccine was not administered appropriately for any reason (**Figure 1**).

Figure 1: Vaccination failure algorithm



[Reference 22 in the report:] Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. Clin Diagn Lab Immunol, 2003, 10(5):780-786.

[Reference 23 in the report:] Cherry JD *et al.* A search for serologic correlates of immunity to Bordetella pertussis cough illnesses. Vaccine, 1998, 16:1901-1906.

Reasons for vaccination failure are manifold and include, but are not restricted to, the following.

A. Vaccine failure. *(1) Vaccinee-related (host-related)*: (a) immunodeficiency; (b) age-related maturation and senescence of immune responsiveness; (c) insufficient or suboptimal immune response; (d) interference due to other infectious agents; (e) waning immunity; (f) suboptimal health status; (g) immunological interference; (h) pre-existing infection with pathogen targeted by the vaccine or immunization during incubation period; and (i) immunosuppressive therapy. *(2) Vaccine-related:* (a) vaccine is not 100% efficacious against included antigens; (b) incomplete coverage of strains, serotypes, genotypes, antigenic variants or escape mutants that can cause a vaccine-preventable disease; (c) antigenic interference or other vaccine-vaccine interactions in case of co-administered vaccines; (d) manufacturing-related.

B. Failure to vaccinate: *(3) Usage issues:* (a) administration error; (b) vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s); (c) storage-related; (d) vaccine beyond expiry date when used. *(4) Immunization programme-related issues:* (a) suboptimal recommendations; (b) shortage of vaccine.

{Some of the detail and examples have been omitted from A and B above.}

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

21. **Vaccine failure** (CIOMS/WHO WG on Vaccine Pharmacovigilance)

Each specific vaccine has a specific prophylactic goal and is used with a specific intent which may be country- or programme-specific. As such, there needs to be a specific definition for vaccine failure which is applicable to that specific vaccine. However, general definitions for vaccine failure can be proposed and confirmed vaccine failure needs to be distinguished from suspected vaccine failure.

{See Clinical vaccine failure and Immunological vaccine failure}

Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

22. **Vaccine hesitancy** (CIOMS WG on Vaccine Safety – VSC)

Vaccine hesitancy is seen in low, middle and high-income countries around the globe. The term refers to delaying acceptance of or refusing vaccines that are on offer. Vaccine hesitancy is complex and situation-specific, varying across time, place and vaccine products.[Reference 37] Although the term vaccine hesitancy has been widely adopted to describe behaviour critical of or hostile to vaccination, it is a catch-all category rather than a coherent concept. [Reference 38] It presumes to cover a very wide range of attitudes and behaviours, influenced by multiple and differential causes and sources, both within individuals and across populations. It seems to imply an unspecified point on a spectrum from extreme opposition to full acceptance, a point which may not represent truly the entire position of an individual or society as a whole. It does not, for example, easily include at the same time the knowledgeable, vaccine-favouring individual or parent who has questions or doubts about a specific vaccine, the parent critically opposed to all vaccines and the generally ill-informed or difficult-to-reach parent whose children are not brought forward for immunization. For the time being, however, this report refers to the term vaccine hesitancy as a shortcut for this range of underlying knowledge, attitudes, practices (KAP) and related concerns and information needs.

[Reference 37 in the report:] Larson HJ, Jarret C, Eckersberger E, Smith DM, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007-2012..

[Reference 38 in the report:] Peretti-Watel P, Larson HJ, Ward JK, Schulz WS, Verger P. Vaccine hesitancy: clarifying a theoretical framework for an ambiguous notion. PLOS Currents Outbreaks. 2015 Feb 25 . Edition 1.

Proposed by: CIOMS Working Group on Vaccine Safety.

23. **Vaccine pharmacovigilance** (CIOMS WG on Vaccine Safety – VSC)

Vaccine pharmacovigilance has been defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

Adopted from: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Vaccine pharmacovigilance (CIOMS WG on Vaccine Safety – AVSS)
Vaccine pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues.
Modified from: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Vaccine pharmacovigilance (CIOMS/WHO WG on Vaccine Pharmacovigilance)
Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

24. **Vaccine product-related reaction** (CIOMS/WHO WG on Vaccine Pharmacovigilance)
{This is one of five cause-specific definitions of an Adverse event following immunization (AEFI). The other four are: Vaccine quality defect-related reaction, Immunization error-related reaction, Immunization anxiety-related reaction and Coincidental event.}

An adverse event following immunization (AEFI) that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

25. **Vaccine quality defect-related reaction** (CIOMS/WHO WG on Vaccine Pharmacovigilance)
{This is one of five cause-specific definitions of an Adverse event following immunization (AEFI). The other four are: Vaccine product-related reaction; Immunization error-related reaction, Immunization anxiety-related reaction and Coincidental event.}

An adverse event following immunization (AEFI) that is caused or precipitated by a vaccine that is due to one or more quality defects [Footnote 1] of the vaccine product including its administration device as provided by the manufacturer.

[Footnote 1 in the report:] For the purpose of this report, a vaccine quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications.
Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

26. **Vaccine quality defect** (CIOMS/WHO WG on Vaccine Pharmacovigilance)
For the purpose of this report, a "vaccine quality defect" is defined as any deviation of the vaccine product as manufactured from its set quality specifications.
Proposed by: CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

27. **Vaccine safety** (CIOMS WG on Vaccine Safety – AVSS)
The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.
Adopted from: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF, accessed 5 May 2021)

28. **Vaccine safety communication** (CIOMS WG on Vaccine Safety – VSC)
Communication about potential risks, demonstrated safety and measures to minimize risks, and programmes to support safe and effective use of vaccines.

Vaccine pharmacovigilance has been defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. Vaccine safety communication is therefore a recognized part of pharmacovigilance.

Proposed by: CIOMS Working Group on Vaccine Safety.

29. **Vaccine safety communication plans (VacSCPs)** (CIOMS WG on Vaccine Safety – VSC)
Topic group 3 of the CIOMS Working Group on Vaccine Safety proposes to define vaccine safety communication plans at country level as "individual vaccine safety communication plans that are specific to vaccine types and the local situation".

Proposed by: CIOMS Working Group on Vaccine Safety.

30. **Vaccine safety communication systems** (CIOMS WG on Vaccine Safety – VSC)
Generally, systems are understood as consisting of structures and processes to fulfil certain objectives; and in order to enable preparing and implementing planned communication, a vaccine safety communication system consists of certain key functions (see **Checklist 5.1**).

Checklist 5.1:

- Development of strategic vaccine-type and situation-specific vaccine safety communication plans (VacSCPs)
- Establishment and maintenance of multistakeholder networks
- Collaboration at local, country, regional and international level
- Monitoring of vaccine knowledge, attitudes, practices (KAP) and related concerns, rumours and information needs
- Interaction with the media through a dedicated spokesperson
- Development of communication messages and materials
- Implementation of communication interventions
- Evaluation of communication interventions
- Management of vaccine safety crisis

Proposed by: CIOMS Working Group on Vaccine Safety.

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