Council for International Organizations of Medical Sciences

CIOMS
CUMULATIVE GLOSSARY

WITH A FOCUS ON PHARMACOVIGILANCE

VERSION 2.3

Geneva 2025

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AUTHORS AND ACKNOWLEDGEMENTS

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, as well as Sanna Hill, Monika Zweygarth and Lembit Rägo from 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. Sanna Hill compiled Version 1.0 of the CIOMS cumulative pharmacovigilance glossary with assistance from Kateriina Rannula. A Glossary Advisory Board was then formed and met periodically to review feedback and prepare further changes. Monika Zweygarth handled ongoing updates, editing and layout from Version 1.1 onwards. CIOMS also thanks Priya Bahri for her useful suggestions for improvements.

DISCLAIMER

The CIOMS cumulative glossary includes CIOMS' recommended definitions for terms used in pharmacovigilance and some related fields, and is for general informational and educational purposes only. Readers are encouraged to verify the original sources for exact wording. Hyperlinks in references are given as in the CIOMS reports from which the definitions originated; however, we cannot keep all hyperlinks in this glossary current on an ongoing basis.

Please also bear in mind that the CIOMS cumulative 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. Nevertheless, as a case in point, where definitions originated from the EU Guideline on good pharmacovigilance practices (GVP), an effort has been made to verify whether the definitions have changed in subsequent revisions. A complete record of the modules, chapters and annexes of the EU GVP Guideline is available on the EMA's GVP webpage. With regard to the guidelines of the International Council for Harmonization (ICH), the CIOMS Glossary of ICH terms and definitions[1] is a useful tool to keep track of evolving definitions.

[1] Freely available at: https://doi.org/10.56759/eftb6868, or from the ICH website at https://ich.org/page/cioms-glossary-ich-terms-definitions

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PREFACE TO THE ANNIVERSARY EDITION (2.2)

As the Council for International Organizations of Medical Sciences (CIOMS) celebrates its 75th anniversary, it looks back on almost four decades of strategic influence in pharmacovigilance and other topics related to medical product development. Co-founded by the World Health Organization (WHO) and UNESCO in 1949, CIOMS is uniquely placed to form a link between intergovernmental organizations, professional groups, the academic world and lay interests. It has defined several widely respected principles and produced a series of detailed guidelines in response to the huge political and technological developments that have been transforming healthcare in the past 75 years.[2]

Pharmacovigilance, i.e. the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems, became systematic and regulated in the 1960s, in the wake of the thalidomide tragedy. By the 1980s the regulatory demand for reporting of adverse drug reactions by pharmaceutical companies had increased, with different requirements in each country. CIOMS was approached to help achieve uniformity in reporting procedures across countries and companies. In 1986 CIOMS convened its first pharmacovigilance working group. The group's consensus resulted in a proposed standardized format— the CIOMS-I reporting form—which was adopted globally.

Subsequent working groups targeted additional emerging aspects of pharmacovigilance. Through the strength of the ideas and credibility of its expert working groups, CIOMS came to drive some of the new thinking about aggregate safety assessments, thus shaping the methodological approach for pharmacovigilance. When the International Council for Harmonisation (ICH) was founded in 1990 to develop harmonized guidelines on regulating pharmaceutical products, the CIOMS recommendations were taken up in several ICH Efficacy (E) Guidelines, forming the basis of modern pharmacovigilance legislation in an increasing number of countries.[3,4]

This glossary reflects the evolving history of pharmacovigilance over the past decades. It compiles all the definitions within the CIOMS reports referenced in the Change history on page ix). 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 in keeping with evolving terminology and/or the context of the respective CIOMS Working Group topic, and some terms have disappeared from use. In this glossary, the current CIOMS definition is emphasised, and definitions from other CIOMS reports have been kept for reference. True synonyms have been

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[2] CIOMS. Organization, Activities, Members. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS); 1994. (PDF)

[3] Ball G, Kurek R, Hendrickson BA, et al. Global Regulatory Landscape for Aggregate Safety Assessments: Recent Developments and Future Directions. Ther Innov Regul Sci. 2020;54(2):447-461. https://doi.org/10.1007/s43441-019-00076-4

[4] Younus MM, Zweygarth M, Rägo L, et al. The Work of the Council for International Organizations of Medical Sciences (CIOMS) in Global Pharmacovigilance. Drug Saf. 2020;43(11):1067-1071. https://doi.org/10.1007/s40264-020-01003-5

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 adopted or modified from. An illustrative example of the visual formats used in this glossary is shown on the next page.

Today, the CIOMS Working Groups continue to act as sounding boards for capturing and disseminating informed opinion on new developments. They bring together some of the world's foremost experts in their fields to develop guidance on topics where knowledge and practice gaps need to be covered worldwide. As some recent CIOMS Working Groups have been dealing with topics extending beyond pharmacovigilance, the glossary is titled *CIOMS cumulative glossary with a focus on pharmacovigilance*. The glossary does not cover CIOMS reports on the subjects of research ethics, clinical pharmacology, standardised MedDRA® queries (SMQs),[5] or publications resulting from CIOMS Roundtable Discussions (1967-1997).

CIOMS is maintaining this glossary on the CIOMS website, where it can be downloaded freely at: https://doi.org/10.56759/ocef1297. Exceptionally, the anniversary edition (preceding this version) was also made available in print in limited numbers; hardcopies can be ordered through the above-mentioned webpage.

We welcome all feedback. Please email your recommendations to info@cioms.ch.

Geneva, Switzerland, August 2024

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

[5] MedDRA® = Medical Dictionary for Regulatory Activities

HOW TO USE THIS GLOSSARY

The example below shows the different visual styles used throughout this glossary to designate different types of information. The current CIOMS definition is emphasised with a heading in colour, and other definitions kept for reference are shown indented, with grey headings. Abbreviations are given in full in each glossary entry, except for some commonly recurring abbreviations (*e.g.* CIOMS, ICH, EU) listed on the next page. Terms and definitions are included as in the respective Working Group report; any additions by the Glossary Advisory Board are shown within braces {}.

Pagination is mostly automatic, so page breaks may occur at awkward places. For any definition, list or table at the end of a page, please check whether it continues on the next page.

Hyperlinks are underlined and can be accessed through the electronic version of this glossary, which is freely available at: https://doi.org/10.56759/ocef1297.

Visual styles

1. Glossary term including synonyms or related terms

CIOMS Working Group report where the definition appears | Translations if any (listed on page xii)

Adopted by: **CIOMS Working Group(s) that adopted the same definition**

Current definition of the term

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

Commentary from the CIOMS Working Group that provided the term and its definition / Information about how different jurisdictions handle the same term. This section may begin with, for example: "In the EU …"

{Comment or explanation added by the Glossary Advisory Board}

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

Earlier/other definition(s):

The term as it appeared in another CIOMS report

CIOMS Working Group report where the definition appeared | Translations if any (listed on page xii)

Adopted by: **CIOMS Working Group(s) that adopted the same definition**

Earlier/other definition of the term

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

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

{Comment or explanation added by the Glossary Advisory Board}

RECURRING ABBREVIATIONS

Art	Article
CIOMS	Council for International Organizations of Medical Sciences
DILI	Drug-induced liver injury
DSUR	Development safety update report
ICH	International Council 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)
MedDRA	Medical Dictionary for Regulatory Activities (ICH)
PSUR	Periodic safety update report
PV	Pharmacovigilance
Rev	Revision
RLS	Resource-limited settings
SCAR	Severe cutaneous adverse reaction
U.S.	United States of America
WG	Working group (CIOMS)
WHO	World Health Organization

CHANGE HISTORY

Glossary Version

Change	Report short name	Reference (see next page)

Version 2.3, published online on 3 July 2025

Terms and definitions added from the following CIOMS Working Group report:

- **CIOMS XII: Benefit-risk balance 2025** [1]
  The report does not have a formal glossary; terms and definitions were identified in the main text in cooperation between the Working Group and the Glossary Advisory Board
- **CIOMS SCAR 2025**
  The report does not have a formal glossary, but some terms and definitions from previous CIOMS reports have been adopted and/or cited in the main text [2]

Definitions of "Signal" re-sequenced, the definition from CIOMS VIII [13] is the current one.

Version 2.2, 75th anniversary edition, published online and as limited print edition in August 2024

Terms and definitions added from the following CIOMS Working Group reports:

- **CIOMS XIII: Real-world data 2024** [3]
  The report does not have a formal glossary; terms and definitions were identified in the main text in cooperation between the Working Group and the Glossary Advisory Board
- **MedDRA Labeling Grouping 2024** [4]

Term added by the CIOMS Glossary Advisory Board: Safety profile

Correction of CIOMS DILI Working Group's definition of 'Number needed to harm (NNH)', last sentence

Version 2.1, published online on 4 May 2023

Terms and definitions added from the following CIOMS Working Group reports:

- **Clinical research in RLS 2021** Definitions were extracted from the text. [6]

Terms added by the CIOMS Glossary Advisory Board: Dechallenge / Rechallenge, Marketing authorization, Immunization stress-related response (ISSR)

Version 2.0, published online on 15 September 2022

Title changed from 'CIOMS Cumulative pharmacovigilance glossary' to 'CIOMS Cumulative glossary with a focus on pharmacovigilance', reflecting the fact that recent CIOMS Working Groups deal with multiple topics related to pharmacovigilance

Terms and definitions added from the following CIOMS Working Group reports:

- **CIOMS XI: Patient involvement 2022** [5]

Terms added by the CIOMS Glossary Advisory Board: Explanatory trial, Low intervention clinical trial

Version 1.1, published online on 3 June 2021

Terms and definitions included from the following CIOMS Working Group reports:

- **CIOMS Vaccine safety communication 2018** [8]
  Definitions were located by searching for the words 'term' and 'definition'/'defined'.
- **CIOMS Vaccine safety surveillance 2017** [9]
- **CIOMS/WHO Vaccine PV terms 2012** [12]
  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 VII: DSUR 2006** [14]
- **CIOMS II: PSUR 1992** [19]

(continued)

Change history (continued)

Version 1.0, published online on 26 March 2021

Terms and definitions included from the following CIOMS Working Group reports:

- CIOMS DILI 2020 [7]
- CIOMS X: Meta-analysis 2016 [10]
- CIOMS IX: Risk minimisation 2014 [11]
- CIOMS VIII: Signal detection 2010 [13]
- CIOMS VI: Clinical trial safety information 2005 [15]
- CIOMS IV: Benefit-risk 1998 [18]

Note: The reports of the CIOMS Working Groups I [20], III [17] and V [16] do not include a formal glossary. No definitions from these reports were included, but some have formed the basis of definitions proposed by subsequent Working Groups (*e.g.* see the term *Development core safety information [DCSI]*).

CIOMS REPORTS REFERENCED

CIOMS Working Group report (most recent on top) **Report short name**

[1] **Benefit-risk balance for medicinal products**. CIOMS Working Group XII report. 2025. https://doi.org/10.56759/gwfz1791 **CIOMS XII: Benefit-risk balance 2025**

[2] **Severe cutaneous adverse reactions (SCAR)**. A consensus by a CIOMS Working Group. 2025. https://doi.org/10.56759/lrty1600 **CIOMS SCAR 2025**

[3] **Real-world data and real-world evidence in regulatory decision making**. CIOMS Working Group XIII report. 2024. https://doi.org/10.56759/kfxh6213 **CIOMS XIII: Real-world data 2024**

[4] **Introduction to MedDRA Labeling Grouping (MLG). A standardised approach to grouping adverse reactions in product safety labels**. Report of the CIOMS MLG Expert Working Group. 2024. https://doi.org/10.56759/hmku5307 **MedDRA Labeling Grouping 2024**

[5] **Patient involvement in the development, regulation and safe use of medicines**. CIOMS Working Group XI report. 2022. https://doi.org/10.56759/iiew8982 **CIOMS XI: Patient involvement 2022**

[6] **Clinical research in resource-limited settings**. A consensus by a CIOMS Working Group. CIOMS, 2021. https://doi.org/10.56959/cyqe7288. **Clinical research in RLS 2021**

[7] **Drug-induced liver injury: Current status and future directions for drug development and the post-market setting.** A consensus by a CIOMS Working Group. 2020. https://doi.org/10.56759/ojsg8296 **CIOMS DILI 2020**

[8] **CIOMS Guide to Vaccine Safety Communication**, 2018. Report by topic group 3 of the CIOMS Working Group on Vaccine Safety. https://doi.org/10.56759/zphi4166 **CIOMS Vaccine safety communication 2018**

[9] **CIOMS Guide to Active Vaccine Safety Surveillance**. Report of CIOMS Working Group on Vaccine Safety. CIOMS, 2017. https://doi.org/10.56759/hnuw8440 **CIOMS Vaccine safety surveillance 2017**

[10] **Evidence Synthesis and Meta-Analysis for Drug Safety.** Report of CIOMS Working Group X. CIOMS, 2016. https://doi.org/10.56759/lela7055 **CIOMS X: Meta-analysis 2016**

[11] **Practical Approaches to Risk Minimisation for Medicinal Products**. Report of CIOMS Working Group IX. CIOMS, 2014. Available here. **CIOMS IX: Risk minimisation 2014**

[12] **Definition and Application of Terms for Vaccine Pharmacovigilance**. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. CIOMS/WHO, 2012. Available here **CIOMS/WHO Vaccine PV terms 2012**

[13] **Practical Aspects of Signal Detection in Pharmacovigilance**. Report of CIOMS Working Group VIII. CIOMS, 2010. Available here. **CIOMS VIII: Signal detection 2010**

[14] **Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials.** Report of CIOMS Working Group VII. CIOMS, 2006. Available here. **CIOMS VII: DSUR 2006**

[15] **Management of Safety Information from Clinical Trials**. Report of CIOMS Working Group VI. CIOMS, 2005. Available here. **CIOMS VI: Clinical trial safety information 2005**

[16] **Current Challenges in Pharmacovigilance: Pragmatic Approaches**. Report of CIOMS Working Group V. CIOMS, 2001. Available here. (Not included)

[17] **Guidelines for Preparing Core Clinical-Safety Information on Drugs**. Second Edition. Report of CIOMS Working Groups III and V. Including New Proposals for Investigator's Brochures. CIOMS, 1999. Available here. (Not included)

[18] **Benefit-risk balance for marketed drugs: Evaluating safety signals**. Report of CIOMS Working Group IV. CIOMS, 1998. Available here. **CIOMS IV: Benefit-risk 1998**

[19] **International Reporting of Periodic Drug-Safety Update Summaries**. Final report of CIOMS Working Group II. CIOMS, 1992. Available here. **CIOMS II: PSUR 1992**

[20] **International Reporting of Adverse Drug Reactions**. Final report of CIOMS Working Group. CIOMS, 1990. Available here. (Not included)

TRANSLATIONS

Report short name	Reference	• Language version(s)
CIOMS VI: Clinical trial safety information 2005	[15]	• Japanese: reference copy on record at the CIOMS Secretariat • Chinese
CIOMS VII: DSUR 2006	[14]	• Japanese: contact RAD-AR Council
CIOMS VIII: Signal detection 2010	[13]	• Chinese • Japanese: contact RAD-AR Council; Amazon
CIOMS IX Risk minimisation 2014	[11]	• Japanese
CIOMS X: Meta-analysis 2016	[10]	• Japanese
CIOMS XI: Patient involvement 2022	[5]	• Japanese: available from the website of the journal *Rinsho Hyoka* (Clinical Evaluation) Vol. 51, Suppl 39, 2024.
CIOMS XIII:Real-world data 2024	[3]	• Chinese

Version 2.1 of this glossary has been translated into Korean, and is freely available here. We gratefully acknowledge the generous support by SELTA SQUARE in making this translation available.

TERMS AND DEFINITIONS:
GENERAL

A

1. Absolute risk

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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. Academia

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The environment or community concerned with research, education, and scholarship.

Modified from: Lexico.com (a collaboration between Dictionary.com and Oxford University Press). Online dictionary accessed on 6 December 2021.

3. Acceptable risk

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The degree of risk (likelihood of an adverse event or outcome) that a person or group is prepared to take or considers reasonable. However, what may be acceptable for one person or group may not be to another.

Proposed by CIOMS Working Group XI.

Earlier/other definition(s):

Acceptable risk

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

4. Active surveillance system

CIOMS DILI 2020

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.

Modified from: CIOMS Working Group VIII.

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

Earlier/other definition(s):

Active surveillance

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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. (PDF)

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).

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

5. Additional risk minimisation measure, synonym: Additional risk minimisation activity; see also Risk minimisation measure and Routine risk minimisation measure

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A risk minimisation measure which is in addition to the routine risk minimisation activities which apply to all medicinal products in a particular region or territory.

Modified from: CIOMS Working Group IX, glossary definition of 'Additional risk minimisation activity'.

Earlier/other definition(s):

Additional risk minimisation activity, see also Routine risk minimisation activities

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

6. Adoption

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

7. Adverse drug reaction (ADR), synonyms: Adverse reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS SCAR 2025** (in-text, with slightly different wording)

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.

Source: Definition EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 3, 08 January 2014).

{Substantially unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5, 26 July 2024), where the definition includes this additional language:

" (... a reasonable possibility.) An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the by healthcare professional or consumer as primary source, it meets the definition of an adverse reaction (see GVP Annex IV, ICH-E2D). Therefore all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the primary source specifically state that they believe the event to be unrelated or that a causal relationship can be excluded. (Adverse reactions may arise…) }

Earlier/other definition(s):

Adverse reaction (AR), synonyms: Adverse drug reaction (ADR), Undesirable effect

MedDRA Labeling Grouping 2024

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: A 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.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Source: 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. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

{In this case, the CIOMS Glossary Advisory Board considers the definition of the CIOMS IX report on Risk minimisation to be the current one, as it corresponds to that in the 2017 and 2024 revisions of Annex I in the EU Guideline on good pharmacovigilance practices (GVP), which are more recent than the source cited above.}.

Adverse drug reaction (ADR)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: 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: DSUR 2006

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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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 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.

8. Adverse event (AE), synonym: Adverse experience

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **MedDRA Labeling Grouping 2024**
CIOMS SCAR 2025 (in-text, with slightly different wording)

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.

Source: EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 3, 08 January 2014).

{Substantially unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5, 26 July 2024), which was updated to include two similar definitions under separate headings, namely:
– "In the context of a clinical trial" (with reference to Regulation (EU) No 536/2014), and
–"In the context of pharmacovigilance and outside a clinical trial"(based on the ICH-E2D Guideline).

In the GVP Annex I, the definition is followed by this commentary:

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

The definition in the CIOMS report on MedDRA Labeling Grouping is sourced from the ICH E6(R2) guideline. It is substantially the same as that of the CIOMS Working Group IX and is followed by the commentary shown above, except that the commentary refers to a "medicinal (investigational) product" instead of a "medicinal product".}*

* 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. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

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

Earlier/other definition(s):

Adverse event (AE)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: 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: DSUR 2006

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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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 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.

9. Adverse event of special interest

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: CIOMS VII: DSUR 2006

{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 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).

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 instruction provided for investigators as to how and when they should be reported to the sponsor.

10. Advocate / Patient advocate

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

{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.

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

11. AGREE Instrument

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A tool that assesses the methodological rigour and transparency in which a guideline is developed.

Source: AGREE Next Steps Consortium (2017). The AGREE II Instrument Electronic version. (PDF)

12. Alert

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

An identified risk associated with the use of medicinal products which requires urgent measures to protect patients.

Proposed by CIOMS Working Group VIII.

13. Analysis of covariance (ANCOVA)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

14. As-started exposure

CIOMS XIII: Real-world data 2024

The as-started exposure definition, which is analogous to the intention-to-treat principle used in RCTs, follows patients from the start of their treatment until the end of follow-up, regardless of treatment discontinuation.

Modified from: Schneeweiss S, Patorno E. Conducting real-world evidence studies on the clinical outcomes of diabetes treatments. Endocrine Reviews. 2021;42(5):658-690. https://doi.org/10.1210/endrev/bnab007

{See also: On-treatment exposure, Time-varying exposure}

B

15. Baseline characteristics

CIOMS DILI 2020

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.

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

16. Bayesian

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

17. Bayesian confidence propagation neural network (BCPNN)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Empirical Bayesian algorithm used for signal detection in spontaneous report databases.

Proposed by CIOMS Working Group VIII.

18. Benefit

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

An estimated gain for an individual or a population.

Source: WHO 2002: The Importance of Pharmacovigilance. (Safety monitoring of medicinal products).

Earlier/other definition(s):

Benefit

CIOMS IV: Benefit-risk 1998

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:[1]

"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."

[1] Benefit, Risk and Cost Management of Drugs. Report of the CPHA National Advisory Panel on Risk/Benefit Management of Drugs. Canadian Public Health Association, January 1993.

Proposed by CIOMS Working Group IV.

19. Benefit-risk balance / benefit-risk profile

CIOMS XII: Benefit-risk balance 2025

The terms benefit-risk profile and benefit-risk balance are used frequently in this report. The term benefit-risk profile is used to refer to a concise description or summary of the potential risks and benefits associated with a medicinal product, which may or may not have undergone a formal benefit-risk assessment, while the term benefit-risk balance is used to refer to the outcome or result of a formal assessment of the potential risks and benefits of a medicinal product.

Proposed by CIOMS Working Group XII.

{The definition is found in the Foreword to the CIOMS Working Group report, see footnote i.}

20. Bias

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

A systematic deviation in results from the truth.

Proposed by CIOMS Working Group X.

21. Binary analysis

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

22. Biomarker

CIOMS DILI 2020

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.

Source: 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)

Earlier/other definition(s):

Biomarker

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

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

23. Bonferroni correction

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

24. Boxed warning ("black box warning")

CIOMS DILI 2020

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).

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)

25. Burden of a risk minimisation activity

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

{See also: Effectiveness of risk minimisation, Risk minimisation-burden balance}

26. Burden to patients

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The additional load that a clinical activity imposes on patients above that which would be experienced under normal clinical practice.

Modified from: CIOMS Working Group IX, glossary definition of 'Burden of a risk minimisation activity'.

C

27. Candidate gene study

CIOMS DILI 2020

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).

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

28. Caregiver

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A person who helps a patient with daily activities, healthcare, or other activities that the patient is unable to perform because of age, illness or disability, and who understands the patient's health-related needs. This person may or may not be a family member and may or may not be paid.

Modified from: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input, Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Department of Health and Human Services Food and Drug Administration. June 2020. (PDF)

29. Case report form (CRF)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: CIOMS DILI 2020

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.

Source: ICH Guideline E6: Good Clinical Practice.

{Unchanged in the ICH Guideline for Good Clinical Practice E6(R2).}

30. Causality assessment

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: CIOMS DILI 2020

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.

{The glossary cited above is no longer available online.}

31. Censored / Censoring

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Earlier/other definition(s):

Censored, or Censoring of data

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

32. Channelling

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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

Source: 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.

33. Chi-square

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

34. CIOMS reportable case histories (CIOMS reports)

CIOMS II: PSUR 1992

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.

35. Civil society

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Communities and groups that work outside of government or commercial bodies.

Modified from: Commission on Social Determinants of Health: Civil Society Report, WHO. October 2007. (PDF)

36. Claims data

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

(In the U.S.) The compilation of information from medical claims that health care providers submit to insurers to receive payment for treatments and other interventions. Medical claims data use standardized medical codes, such as the World Health Organization's International Classification of Diseases Coding (ICD-CM), to identify diagnoses and treatments.

Source: U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. December 2018. (PDF)

{ICD-10-CM is an adaptation of ICD-10 for use in the United States for U.S. government purposes. Its development has been authorized by WHO. See details at: CDC National Center for Health Statistics. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). (Webpage as last reviewed 6 April 2022).}

37. Clinical development

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The research performed in humans that increases knowledge about the safety and efficacy of a medicine in a particular indication.

Proposed by CIOMS Working Group XI.

38. Clinical development plan

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A master document which outlines the research strategy to progress a medicine from first in human to authorisation.

Proposed by CIOMS Working Group XI.

39. Clinical endpoint

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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

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

40. Clinical practice guidelines, synonym: Clinical guidelines

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Recommendations on how to prevent, diagnose and/or treat a medical condition. A clinical practice guideline should summarise current medical knowledge, the pros and cons of the scientific evidence supporting different options and how the authors reached their recommendation.

Modified from: InformedHealth.org, Institute for Quality and Efficiency in Health Care (IQWiG, Germany). What are clinical practice guidelines? (Webpage as updated 8 September 2016)

41. Clinical trial

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A research study, in a defined and controlled setting, where participants are assigned prospectively to one or more (or no) interventions to evaluate the effects of the intervention on biomedical or health-related outcomes. The research is performed according to a written protocol. The intervention may be a medicine, vaccine, device, diagnostic or surgical procedure, or change in behaviour (*e.g.* diet).

Modified from: ClinicalTrials.gov. Glossary of Common Site terms. Definition of 'Interventional study (clinical trial)'. (Webpage as last reviewed October 2021)

Earlier/other definition(s):

Clinical study

Clinical research in RLS 2021

A research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two broad types of clinical studies: interventional studies (also called clinical trials) and observational studies.

Source: ClinicalTrials.gov. Glossary of Common Site terms. Definition of 'Clinical study' (Webpage accessed 3 April 2023)

{The definition is found in Section 1.3 of the CIOMS Working Group report}

Clinical trial/clinical study

CIOMS VII: DSUR 2006

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).

{Unchanged in the ICH Guideline for Good Clinical Practice E6(R2).}

42. Cohort event monitoring (CEM)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. *{This glossary is no longer available online.}*

43. Cohort study (prospective / retrospective)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Strom, BL. Pharmacoepidemiology. 4th ed., Wiley. 2005, p. 23.

44. Company core data sheet (CCDS)

MedDRA Labeling Grouping 2024

A document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.

Source: ICH Harmonised Tripartite Guideline. Periodic Benefit-Risk Evaluation Report (PBRER). E2C(R2). 17 December 2012. Available at: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

45. Company core safety information (CCSI)

CIOMS VII: DSUR 2006

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.

Source: 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.

Earlier/other definition(s):

Company core safety information (CCSI)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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).

46. Compassionate use

CIOMS VII: DSUR 2006

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.

47. Completed clinical trial

CIOMS VII: DSUR 2006

Study for which a final clinical study report is available.

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.

48. Composite endpoint

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

49. Confidence interval (CI)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

50. Conflict of interest

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A situation where a person's judgement, decision or action may be unduly influenced (or seen to be influenced) by circumstances such as the person's or family member's employment, investments, scientific work or invention.

Proposed by CIOMS Working Group XI.

51. Confounding

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

52. Confounding by indication

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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).

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

53. Consensus techniques

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Methods or processes used to reach agreement, or a mutually acceptable solution, between a group of individuals.

Modified from: American Heart Association: Consensus-Based Decision-Making Processes. (PDF accessed 6 December 2021).

{Link no longer valid as at 15 July 2022. Alternative source: The Consensus Council, Inc. agree.org. Consensus-Based Decision-Making Processes. PDF (undated), accessed 5 July 2022.}

54. Context of use (COU)

CIOMS DILI 2020

(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.

Source: 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.

Source: 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)

55. Contingency Table

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

56. Contract research organisation (CRO)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Research organisation

57. Core data sheet (International prescribing information)

CIOMS II: PSUR 1992

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.

58. Correlation

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

59. Covariance

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

60. Covariate

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

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

Earlier/other definition(s):

Covariate

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

61. Coverage

CIOMS IX: Risk minimisation 2014

See Reach

62. Cox model

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

63. Cross-sectional study, prevalence study, see also Survey

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

64. Crude pooling

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

65. Cumulative meta-analysis

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Source: Glossary of Terms in The Cochrane Collaboration. Version 4.2.5, May 2005. (PDF)

66. Current practice, see also Normal clinical practice

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A diagnostic, monitoring, or therapeutic procedure can be considered current practice in a particular geographic area if at least one of the following is fulfilled:

- Routinely performed by a proportion of healthcare professionals and is not deemed obsolete;
- Performed according to evidence based medicines criteria;
- Defined in guidelines issued by a relevant medical body;
- Mandated by regulatory and/or medical authorities;
- Reimbursed by the national or private health insurance.

Current practice may or may not be considered as Standard of care.

Modified from: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCEPP considerations on the definition of non-interventional trials under the current legislative framework ('clinical trials directive' 2001/20/EC). 22 November 2011. (PDF)

D

67. Data and safety monitoring board (DSMB)

{See Independent data monitoring committee (IDMC)}

68. Data lock point for DSUR

CIOMS VII: DSUR 2006

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.

Earlier/other definition(s):

Data lock-point (Cut-off date)

CIOMS II: PSUR 1992

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.

69. Data mining

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: CIOMS DILI 2020

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.

70. Data monitoring committee (DMC)

{See Independent data monitoring committee (IDMC)}

71. Dechallenge / Rechallenge

CIOMS Glossary Advisory Board, April 2023

Dechallenge is the withdrawal of a drug from a patient to observe whether an adverse event (AE) continues.

If the AE continues, this is designated a negative dechallenge, and a causal relationship is less likely.

If the AE decreases in severity or disappears, this is designated a positive dechallenge, and a causal relationship is more likely.

Rechallenge is the reintroduction of the drug to the patient.

If the AE reappears, this is designated a positive rechallenge and strongly suggests a causal relationship.

If the AE does not reappear, this is designated a negative rechallenge, and suggests there is no causal relationship.

Partial dechallenge is a reduction of the drug dose to observe whether an adverse event continues or not.

Partial rechallenge is a gradual reintroduction of the drug to observe whether the AE reappears or not.

Note: In its report, the CIOMS Working Group stated that rechallenge should only be carried out intentionally "when there is likely to be clinical benefit to the patient. Thus, only if in the judgment of the treating physician the anticipated result is directly relevant to the patient's treatment and well being should that individual be rechallenged." (Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. CIOMS; 2001: page 131-132.)

Proposed by the CIOMS Glossary Advisory Board.

72. Designated medical event (DME)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: Hauben M *et al*. The role of data mining in pharmacovigilance. Expert Opinion in Drug Safety, 2005, 4:929-948.

73. Development core safety information (DCSI)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: **CIOMS VII: DSUR 2006**

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.

74. Development international birth date (DIBD)

CIOMS VII: DSUR 2006

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}

75. Development pharmacovigilance and risk management plan (DPRMP)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: **CIOMS VII: DSUR 2006** under the heading '**Development pharmacovigilance and risk management plan (DPRMP) or Development risk management plan (DRMP)**'

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.

76. Development safety update report (DSUR)

CIOMS VII: DSUR 2006

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.

Earlier/other definition(s):

Development safety update report (DSUR)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

77. Direct healthcare professional communication (DHPC)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: 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 5, 26 July 2024). 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."}

78. Disability-adjusted life year (DALY)

Clinical research in RLS 2021

The sum of years lost due to premature death and years lived with disability. DALYs are also defined as years of healthy life lost.

Source: Institute for Health Metrics Evaluation. Global Health Data Exchange. Online Glossary, accessed 3 April 2023.

{The definition is found in Figure 1 of the CIOMS Working Group report}

79. Disease outbreak

Clinical research in RLS 2021

The World Health Organization defines a disease outbreak as follows: "A disease outbreak is the occurrence of disease cases in excess of normal expectancy. The number of cases varies according to the disease-causing agent, and the size and type of previous and existing exposure to the agent."

Source: World Health Organization. Environment, Climate Change and Health. Disease Outbreaks. (Webpage, last accessed 3 April 2023)

{The definition is found in Appendix 3 of the CIOMS Working Group report}

80. Disproportionality analysis/Analysis of disproportionate reporting

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**

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.

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

81. Diversity

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The degree to which individuals in a group (*e.g.* participants in a trial) have differences in characteristics such as age, race, gender, and disease severity. Diversity may also relate to individuals with differing beliefs, customs, habits, or social and economic status.

Proposed by CIOMS Working Group XI.

82. Dominant risk

CIOMS IV: Benefit-risk 1998

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.

83. Drug-event pair

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

A combination of a medicinal product and an adverse event which has appeared in at least one case report entered in a spontaneous report database.

Proposed by CIOMS Working Group VIII.

E

84. Ecological bias (also known as Ecological fallacy)

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

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

85. Economic outcomes

CIOMS XIII: Real-world data 2024

Outcomes that measure the economic impact of an intervention or exposure.

Proposed by CIOMS Working Group XIII.

{See also: Patient-reported outcome, Surrogate outcomes}

86. Educational tool

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Material designed to impart awareness, knowledge and aid comprehension of specific information.

Proposed by CIOMS Working Group IX.

87. Effect modifier

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Source: Dodge, Y, The Oxford Dictionary of Statistical Terms, 6th ed., International Statistical Institute, New York. Oxford University Press, Inc., 2006.

88. Effectiveness

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Extent to which an intervention when used under the usual clinical circumstances does what it is intended to do for a defined population.

Source: Hartzema AG, Porta MS, Tilson HH. Pharmacoepidemiology: An introduction. 2nd Edition. Harvey Whitney Books. 1991.

Earlier/other definition(s):

Effectiveness

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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: Benefit-risk 1998

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).[1]

[1] 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.

89. Effectiveness of risk minimisation

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

{See also: Burden of risk minimization activity, Risk minimisation-burden balance}

90. Effectiveness threshold

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

91. Efficacy

CIOMS IV: Benefit-risk 1998

Adopted by: **CIOMS VI: Clinical trial safety information 2005** | (Chinese translation available, see page xii)

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.

Proposed by CIOMS Working Group IV.

Note {CIOMS IV}: 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.

Commentary (CIOMS VI): 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.

92. Efficiency

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Results achieved in relation to the resources invested.

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

93. E-health

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

E-health is defined as the cost-effective and secure use of information and communication technology (ICT) in support of health and health-related fields, which include health-care services, health surveillance, health literature, and health education, knowledge and research.

Modified from: Fifty-eighth World Health Assembly. Resolution 58.28 (WHA58.28). e-health, 2005. (PDF)

{The definition is found in the CIOMS Working Group XI report in section 5.3.1, footnote i.}

Earlier/other definition(s):

eHealth

Clinical research in RLS 2021

The World Health Organization (WHO) defines eHealth as "the use of information and communication technologies (ICT) for health".[1]

{From: WHO. Digital health research. Webpage, accessed 3 April 2023.}

[1] The full definition given in World Health Assembly (WHA) Resolution 58.28 is: "eHealth is the cost-effective and secure use of ICT in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research."

Source: Resolution WHA58.28. eHealth. In: Fifty-eighth World Health Assembly, Geneva, 16–25 May 2005. Resolutions and decisions, Annex. Geneva: World Health Organization; 2005:108. (PDF)

{The definition is found in Appendix 2 of the CIOMS Working Group report}

94. Electronic health records (EHRs)

Clinical research in RLS 2021

In its third global survey on eHealth, WHO has defined EHRs as "real-time, patient-centred records that provide immediate and secure information to authorized users. EHRs typically contain a patient's medical history, diagnoses and treatment, medications, allergies, immunizations, as well as radiology images and laboratory results".

Source: WHO. Global diffusion of eHealth: Making universal health coverage achievable. Report of the third global survey on eHealth. Global Observatory for eHealth. Geneva, Switzerland: World Health Organization; 2016. (PDF)

{The definition is found in Appendix 2B of the CIOMS Working Group report}

95. Emerging data sources

CIOMS XIII: Real-world data 2024

The introduction of new technologies such as those related to remote care and the increased use of mobile devices has provided new sources of information that can be generated with unprecedented volume, speed and complexity, and require a different set of data management and analytical methods. Although the current use of these emerging sources is still limited compared to the traditional ones, with the rapid development of modern computing and advanced analytics, it is just a matter of time before they will also be used as key real-world data (RWD) sources in the context of regulatory decision making.

{See also Traditional data sources}

96. Endpoint

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

In clinical trials, an event or outcome that can be measured to determine how beneficial and/or harmful an intervention is.

Modified from: National Institutes of Health, National Cancer Institute. (Online dictionary accessed 6 December 2021).

Earlier/other definition(s):

Endpoint

CIOMS DILI 2020

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.

Source: 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: Meta-analysis 2016 | (Japanese translation available, see page xii)

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 Working Group X. Modified from ICH International Conference on Harmonisation. ICH E9 Statistical principles for clinical trials ICH Harmonised Tripartite Guideline. 1995.

97. Endpoint prioritisation

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The process that guideline developers go through to decide which endpoints in a study or trial are most important. Importance is determined by the question being asked.

Proposed by CIOMS Working Group XI.

98. Epidemiology

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Epidemiology is the study, in populations or defined groups of individuals, into how, how often, when and why health-related events occur.

Proposed by CIOMS Working Group XI.

99. Epigenomics

CIOMS DILI 2020

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.

Source: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage accessed March 2020)

100. Evaluation of drug-induced serious hepatotoxicity (eDISH) plot

CIOMS DILI 2020

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.

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)

101. Evidence-based medicine

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The conscientious, explicit and judicious use of current best scientific evidence in making decisions about the care of individual patients.

Modified from: Sackett DL *et al.* Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71. doi: 10.1136/bmj.312.7023.71

102. Expected and Unexpected adverse drug reaction

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: **CIOMS VII: DSUR 2006** under the heading **'Expected and Unexpected adverse drug reaction (See also Listed and Unlisted)'**

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).

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 drug or package insert/summary of product characteristics for an approved product).

Source: ICH Guideline: E6 Good Clinical Practice

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).

{CIOMS VI} 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.

{CIOMS VII} 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.

103. Explanatory trial

CIOMS Glossary Advisory Board, September 2022

A study designed to assess the effects of a treatment given in a well-defined and controlled setting.

Proposed by the CIOMS Glossary Advisory Board. Modified from: Glossary of Evaluation Terms for Informed Treatment choices (GET-IT). CC BY-SA 4.0. Online glossary, accessed 25 August 2022.

See also: Clinical trial

F

104. Failure modes and effects analysis (FMEA)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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. Failure Modes and Effects Analysis (FMEA) Tool. (Webpage, accessed 16 Jun 2013)

105. Fairweather Rules

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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).

106. False negative

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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}

107. False positive

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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}

108. Family caregiver

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Caregiver

109. Fisher's exact test

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

110. Fixed effects

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

111. Forest plot

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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. Version 4.2.5, May 2005. (PDF)

112. Frequentist statistics

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Probabilities viewed as a long term frequency with an assumption of a repeatable experiment or sampling mechanism.

Proposed by CIOMS Working Group VIII.

G

113. Genome-wide association study (GWAS)

CIOMS DILI 2020

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.

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

114. Genomics

CIOMS DILI 2020

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.

Source: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage accessed March 2020)

115. Good Clinical Research Practice (GCP)

Clinical research in RLS 2021

A process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects.

Source: WHO. Handbook for good clinical research practice (GCP): guidance for implementation. Geneva, Switzerland: World Health Organization; 2015. (WHO Institutional Repository for Information-Sharing)

{The definition is found in section 3.2 of the CIOMS Working Group report}

H

116. Harm

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Damage qualified by measures of frequency of occurrence, severity or duration.

Source: Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety. 2007, 30: 825–830.

117. Hazard

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

A situation or given factor that under particular circumstances could lead to harm. A source of danger.

Modified from: CIOMS Working Group IV.

Earlier/other definition(s):

Hazard

CIOMS IV: Benefit-risk 1998

Adopted by: CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

A situation that under particular circumstances could lead to harm. A source of danger.

Proposed by CIOMS Working Group IV.

118. Health literacy

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An individual's capacity to access, understand, appraise, and apply health information.

Modified from: Sørensen K, Van den Broucke S, Fullam J, et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health. 2012;12:80. doi: 10.1186/1471-2458-12-80

119. Health-related quality of life (HRQoL)

CIOMS XIII: Real-world data 2024

HRQoL measures the impact of disease and treatment on patients' lives and is defined as "the capacity to perform the usual daily activities for a person's age and major social role",[1] and often includes physical functioning, psychological well-being, and social role functioning.

[1] Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Annals of Internal Medicine. 1993;15;118(8):622-629. https://doi.org/10.7326/0003-4819-118-8-199304150-00009

Modified from: Velentgas P, Dreyer NA, Wu AW. Outcome Definition and Measurement. In: Velentgas P, Dreyer NA, Nourjah P, et al., editors. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Jan. Chapter 6. Available from: https://www.ncbi.nlm.nih.gov/books/NBK126186/

120. Health technology

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Any intervention to promote health, prevent, diagnose or treat disease, or for rehabilitation or long-term care. This includes medicines, vaccines, devices, procedures and organisational systems used in health care.

Modified from: EUPATI. Health Technology Assessment: Key Definitions. (Webpage accessed 8 October 2021).

121. Health technology assessment

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Adopted by: **CIOMS XII: Benefit-risk balance 2025**

Health technology assessment is a multidisciplinary process to determine the relative value of an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system.

Modified from: International Network of Agencies for Health Technology Assessment (INAHTA). (Webpage accessed 16 January 2022)

{And see the HTA Glossary at http://htaglossary.net/HomePage, accessed 15 July 2022}

122. Healthcare professional (HCP) (also: Health professional)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **MedDRA Labeling Grouping 2024**

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.

Combined and 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).

123. Healthcare system

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An organised structure designed to promote, restore or maintain health in populations defined by geographical region, insurance coverage or employment.

The term is frequently used to mean how services are provided to the population of a particular country.

Proposed by CIOMS Working Group XI.

124. Heterogeneity

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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

Proposed by CIOMS Working Group 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.

125. Hy's law

CIOMS DILI 2020

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.

Based on: U.S. FDA. Guidance for Industry. Drug-induced livery injury: premarketing clinical evaluation. (PDF)

I

126. Identified risk

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS SCAR 2025** (without the examples)

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.

Source: 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 5, 26 July 2024). Note: The GVP definition in Annex I includes an additional sentence: "Adverse reactions included in section 4.8 of the summary of product characteristics (SmPC) are also considered identified risks, unless they are class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product (these would normally be considered as a potential risk).}

Earlier/other definition(s):

Identified risk

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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

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

Identified risk

CIOMS VII: DSUR 2006

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.

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

127. Idiosyncratic DILI (IDILI)

CIOMS DILI 2020

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.

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)

{See also Intrinsic DILI}

128. Implementation

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

129. Implementation fidelity

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

The degree to which an intervention or programme is delivered as intended.

Source: Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implement Sci. 2007;2:40. Published 2007 Nov 30. doi:10.1186/1748-5908-2-40

130. Important identified risk and Important potential risk

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS SCAR 2025**

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.}

Earlier/other definition(s):

Important identified risk, Important potential risk or Important missing information

CIOMS VII: DSUR 2006

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.

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

131. Important missing information, see Missing information

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

132. Incidence

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

{Not to be confused with: Prevalence}

133. Independent data monitoring committee (IDMC), or Data and safety monitoring board (DSMB), or Monitoring committee, or Data monitoring committee (DMC)

CIOMS VII: DSUR 2006

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.

Source: 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.

*{The definition in the ICH E6(R3) Guideline has been slightly updated (changes in bold): "An independent data monitoring committee **(e.g., data safety monitoring board)** that may be established by the sponsor to assess at intervals the progress of a clinical trial, the **safety and relevant efficacy data**, and to recommend to the sponsor whether to continue, modify or stop a trial.}*

Earlier/other definition(s):

Data Monitoring Committee (DMC)

CIOMS XII: Benefit-risk balance 2025

The definition of a DMC: 'a group of individuals who review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make a benefit-risk assessment'.

Source: Evans SR, Bigelow R, Chuang-Stein C, Ellenberg SS, Gallo P, He W, Jiang Q, Rockhold F. Presenting risks and benefits: helping the data monitoring committee do its job. Annals of Internal Medicine. 2020;21;172(2):119-125. https://doi.org/10.7326/M19-1491

{The definition is found in Table 11 CIOMS Working Group report, see footnote i.}

Independent data-monitoring committee (IDMC) or Data and safety monitoring board (DSMB), or Monitoring committee, or Data monitoring committee

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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.

134. Independent ethics committee (IEC), see also Institutional review board

CIOMS VII: DSUR 2006

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).

Source: 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.

Earlier/other definition(s):

Independent ethics committee (IEC) (Also, see Institutional review board)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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.

135. Indicator

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

136. Individual case safety report (ICSR)

MedDRA Labeling Grouping 2024

The complete information provided by a reporter at a certain point in time to describe an event or incident of interest. The report can include information about a case involving one subject or a group of subjects. [27953 Human Pharmaceutical Reporting].

Source: ICH E2B Implementation Working Group. Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs). E2B(R3). Data Elements and Message Specification. Version 5.02, 10 November 2016. Available at: https://admin.ich.org/sites/default/files/inline-files/E2B%28R3%29_IG_Complete_Package_v1_09.zip, filename: 1_ICH_ICSR_Implementation_Guide_v5_02.pdf

The citation in square brackets in the above definition refers to the following document: ISO/HL7 27953-2:2011. Health informatics — Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR. Available at: https://www.iso.org/standard/53825.html

{The definition provided above comes from a guide for implementing international good pharmacovigilance practices. The EU Good Pharmacovigilance Practice (GVP) definition of an ICSR is as follows:

> ***Individual case safety report (ICSR); synonym: Adverse (drug) reaction report***
> *Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.*
>
> *European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5, 26 July 2024).}*

137. Individual participant data

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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)

138. Industry, pharmaceutical

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Companies whose primary functions include one or more of the following: research, development, manufacture, and marketing of medicines and/or vaccines.

Proposed by CIOMS Working Group XI.

Note: In this report, we use 'Industry' and 'Pharmaceutical industry' interchangeably.

139. Informational tool

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Material that is applied to bring attention or focus on information relevant to meeting risk minimization objectives.

Proposed by CIOMS Working Group IX.

140. Informed assent, see also Informed consent

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Informed assent means that a child or adolescent who will possibly participate in a research study is meaningfully engaged in the research discussion in accordance with their capacities. Assent must be considered as a process, and is partnered with the informed consent acquired from the parents or legal guardian; it is not merely the absence of dissent. It is of major importance to inform the child or adolescent and obtain assent preferably in writing at an age-appropriate level for children who are literate. The process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation.

Informed assent can be applied to adults who do not have the legal capability to give consent.

Modified from: CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. 2016. (PDF)

141. Informed consent, see also Informed assent

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A process by which a potential participant (or a responsible proxy – *e.g.* a parent) voluntarily confirms willingness to take part in a study, after having been informed of all aspects of the study relevant to the person's decision to participate. This must be recorded in the appropriate format.

A type of informed consent is sometimes used as a risk minimisation tool for an authorised medicine to ensure that the patient has had the potential risks of the treatment, and other important information, explained to them by the healthcare professional who is prescribing, dispensing or using it.

Modified from: ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice. E6(R2). International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. (PDF)

Earlier/other definition(s):

Informed consent

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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.

142. Institutional review board (IRB), see also Independent ethics committee (IEC)

CIOMS VII: DSUR 2006

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.

Earlier/other definition(s):

Institutional review board (IRB), see also Independent ethics committee (IEC)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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}

143. Integrated summary of safety (ISS)

MedDRA Labeling Grouping 2024

Integrated summary of safety is a document that is included in the submission of new drug applications in some jurisdictions such as the United States. This document contains detailed integrated analyses of all relevant data from the clinical study reports on the drug.

Modified from: U.S. FDA. Guidance for Industry. Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. April 2009. Available at: https://www.fda.gov/media/75783/download

144. International birth date

CIOMS II: PSUR 1992

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.

{See also Development international birth date (DIBD)}

145. International prescribing information

CIOMS II: PSUR 1992

See Core data sheet

Proposed by CIOMS Working Group II.

146. Interoperability

Clinical research in RLS 2021

Interoperability has been defined as "the ability of different information systems, devices or applications to connect, in a coordinated manner, within and across organizational boundaries to access, exchange and cooperatively use data amongst stakeholders, with the goal of optimizing the health of individuals and populations."

Source: Healthcare Information and Management Systems Society, Inc. HIMSS. Interoperability in Healthcare. (Webpage, accessed 3 February 2021)

{The definition is found in Appendix 2B of the CIOMS Working Group report}

{Note: The definition on the above-mentioned webpage had evolved as of 3 April 2023. Readers are encouraged to look at the latest version.}

147. Interventional clinical trial, see also Non-interventional clinical trial

CIOMS VII: DSUR 2006

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.

Source: 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}

148. Intrinsic DILI

CIOMS DILI 2020

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).

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)

{See also Idiosyncratic DILI}

149. Investigational product, synonym: investigational medicinal product

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A medicine, vaccine or placebo which is being tested, or used as a comparison, in a clinical trial.

Modified from: European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Article 2(2)(5) (PDF)

Earlier/other definition(s):

Investigational drug

CIOMS VII: DSUR 2006

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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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.

150. Investigator's brochure (IB)

MedDRA Labeling Grouping 2024

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants.

{An IB is updated as new information becomes available.}

Source: 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. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Note: Also see Appendix A. Investigator's Brochure, in the draft revised ICH guideline E6(R3) referenced below; the definition itself has remained unchanged from the ICH E6(R2) guideline.

ICH Harmonised Guideline. Good Clinical Practice (GCP). E6(R3). Draft version, endorsed on 19 May 2023. Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2023. Available at: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

K – L

151. Kaplan-Meier

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

152. Labelled or Unlabelled, see also Expected and Unexpected adverse drug reaction

CIOMS VI: Clinical trial safety information 2005) | (Chinese translation available, see page xii)

Adopted by: **CIOMS VII: DSUR 2006**

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 a reaction being labelled or unlabelled was discussed in the report. Please see the report index.}

153. Labelling

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**
MedDRA Labeling Grouping 2024

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).

{Unchanged in the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5, 26 July 2024)}

154. Large simple trial

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A prospective randomised study to detect the effects of an intervention under the usual conditions in which it will be used. Large simple trials generally meet the following conditions:

- Study conducted at the sites and under the conditions in which it will be used once available;
- Participants reflect the general population who would be eligible for the intervention with minimal inclusion and exclusion criteria;
- Size large enough to detect small but clinically significant differences between the groups;
- Outcome easily and objectively measured with resources normally available to those treating patients;
- Data collection amount and timing follows normal clinical practice.

Proposed by CIOMS Working Group XI.

155. Legacy product

CIOMS XII: Benefit-risk balance 2025

Legacy products refer to medicinal products previously approved prior to current day regulatory requirements.

Proposed by CIOMS Working Group XII.

{The definition is found in the Foreword to the CIOMS Working Group report, see footnote iv.}

156. Listed/Unlisted, see also Expected and Unexpected adverse drug reaction

CIOMS VII: DSUR 2006

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.

Earlier/other definition(s):

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

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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 a reaction 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

157. Low- and middle-income countries (LMIC)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Countries with gross national income (GNI) per capita below a set threshold, which is defined periodically, using GNI data from the World Bank, by the Development Assistance Committee of the Organisation for Economic Co-operation and Development.

Modified from: Organisation for Economic Co-operation and Development (OECD): Development Assistance Committee (DAC) list of Official Development Assistance (ODA) recipients. (Webpage accessed 16 January 2022)

158. Low-intervention clinical trial

CIOMS Glossary Advisory Board, September 2022

'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

  (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

  (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Source: European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Article 2(2)(3). (PDF)

M

159. Maintenance

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.}*

160. Manufacturer, pharmaceutical

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A legal entity (*e.g.* pharmaceutical company) that is engaged in the industrial scale synthesis, formulation, production or preparation of pharmaceuticals and/or vaccines.

Proposed by CIOMS Working Group XI.

161. Marketing authorisation

CIOMS Glossary Advisory Board, April 2023

Permission, granted by a regulatory authority, to market or distribute a specified medicinal product in its territory. This usually occurs after scientific evaluation of the product's safety, efficacy and quality.

Proposed by the CIOMS Glossary Advisory Board.

162. Marketing authorisation applicant (MAA)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A company or other legal entity seeking authorisation from a regulatory authority to market a medicine or a vaccine in a national or regional territory.

Modified from: European Medicines Agency, About us, Glossary of regulatory terms: 'Marketing authorisation holder'. (Webpage accessed 10 December 2021)

163. Marketing authorisation holder (MAH)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Adopted by: **CIOMS XIII: Real-world data 2024**

A company or other legal entity that has been granted permission by a regulatory authority to market a medicine or a vaccine in a national or regional territory.

Modified from: European Medicines Agency, About us, Glossary of regulatory terms: 'Marketing authorisation holder'. (Webpage accessed 10 December 2021) {Web address no longer valid}

{Note: CIOMS prefers this definition to the one shown below because the term "Marketing authorisation holder" is used globally.}

Earlier/other definition(s):

Marketing authorisation holder (MAH)

MedDRA Labeling Grouping 2024

The company or other legal entity that has the authorisation to market a medicine in one, several or all European Union Member States.

Source: European Medicines Agency, About us, Glossary of regulatory terms: "Marketing authorisation holder". Available at: https://www.ema.europa.eu/en/glossary/marketing-authorisation-holder, last accessed 4 March 2024.

164. MedDRA (Medical Dictionary for Regulatory Activities)

CIOMS VII: DSUR 2006

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)

{See also: MedDRA hierarchy, MedDRA Labeling Grouping (MLG), Standardized MedDRA query (SMQ)}

165. MedDRA hierarchy

MedDRA Labeling Grouping 2024

MedDRA terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The structure of MedDRA is hierarchical. There are five levels to the MedDRA hierarchy, arranged from very specific to very general.

- Lowest Level Terms (LLTs)
- Preferred Terms (PTs)
- High Level Terms (HLTs)
- High Level Group Terms (HLGTs)
- System Organ Classes (SOC)

Source: MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy , accessed 10 November 2022.

{The report on MedDRA Labeling Grouping also includes definitions of each of the five MedDRA hierarchy levels, as described on the webpage cited above.}

166. MedDRA Labeling Grouping (MLG)

MedDRA Labeling Grouping 2024

MLGs are groupings of near-synonymous MedDRA Preferred Terms (PTs) that convey substantially similar clinical concepts.

Source: Große-Michaelis I, Proestel S, Rao RM, et al. MedDRA Labeling Groupings to Improve Safety Communication in Product Labels. Ther Innov Regul Sci. 2023;57(1):1-6. https://doi.org/10.1007/s43441-022-00393-1

MedDRA = Medical Dictionary for Regulatory Activities

{Notes:

(1) Clarification, from the Executive Summary of the report on MedDRA Labeling Grouping (under "Background and problem statement"):

"MedDRA does not currently provide groupings of adverse reaction terms conveying the same medical concept that are intended for use in product safety labels (PSLs). (…) Therefore, there is a need to combine adverse reaction terms that describe the same concepts. To fulfil this need, some institutions have developed their own groupings, but in the absence of agreed conventions, this has inevitably led to considerable variability in approaches. The CIOMS Expert Working Group was established to develop international consensus principles for a new type of groupings, termed MedDRA Labeling Groupings (MLGs)."

(2) The MedDRA Labeling Grouping report also defines two related terms: "Custom grouping" (i.e. the groupings developed by some institutions, as mentioned in the above paragraph), and "MedDRA Labelling Entity" (a former naming idea for "MedDRA Labeling Grouping".}

(3) See also: Standardized MedDRA queries (SMQ)}

167. Medication guide

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Printed document supplied with many prescription medicines that contains U.S. FDA-approved information on particular issues and that can help patients avoid serious adverse events.

Modified from: U.S. FDA website. Drug safety and availability. Medication Guides. (Webpage, content current as of 3 January 2020)

Earlier/other definition(s):

Medication guide (Med guide or MG)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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: U.S. FDA website. Drug safety and availability. Medication Guides. Webpage, accessed 17 March 2013.

168. Medicinal product

CIOMS XIII: Real-world data 2024

A substance or combination of substances, including any biological product, intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

Modified from: European Medicines Agency (EMA). Glossary of Regulatory Terms. Available at: https://www.ema.europa.eu/en/glossary/medicinal-product, accessed 10 May 2024.

{The CIOMS XIII report uses the plural: "Medicinal products are defined as substances…"}

Earlier/other definition(s):

Medicinal product

CIOMS XII: Benefit-risk balance 2025

In this report, medicinal products are considered to include prescription and non-prescription pharmaceuticals and biologicals including vaccines.

Proposed by CIOMS Working Group XII.

{The definition is found in the Foreword to the CIOMS Working Group report, see footnote ii.}

Medicinal product

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)
Adopted by: CIOMS SCAR 2025

Any substance or combination of substances:

- presented as having properties for treating or preventing disease in humans; or
- which may be used in or administered to humans either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Modified from: European Parliament. Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (PDF) Article 1(2).

Note: In other jurisdictions, this may be called a medicine, medical product or a drug, and may include biologicals and vaccines.

169. Medicine life-cycle

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The time between the first discovery of a potential medicine to when the medicine, once developed, is no longer available to patients.

Proposed by CIOMS Working Group XI.

170. Medicine or vaccine use within label, synonym: On-label use;

See also antonym: Off-label use

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Use of a medicinal product in accordance with the terms of the marketing authorisation.

Proposed by CIOMS Working Group XI.

{This definition is also included in the Vaccine section of this glossary.}

171. Medicines developer

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The company/institution that is responsible for, and may perform, the research necessary to get the evidence needed for the medicine to be authorised and made available to patients.

Proposed by CIOMS Working Group XI.

172. Meta-analysis

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Earlier/other definition(s):

Meta-analysis

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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

173. Metabolomics

CIOMS DILI 2020

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.

Source: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage accessed March 2020)

174. Meta-regression

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Source: Glossary of Terms in the Cochrane Collaboration. Version 4.2.5, May 2005. (PDF)

175. M-health (mobile health)

CIOMS XI: Patient involvement 2022

World Health Organization defines m-health as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices".

Source: WHO Global Observatory for eHealth. mHealth: new horizons for health through mobile technologies: second global survey on eHealth. Geneva, Switzerland: World Health Organization, 2011. (PDF)

{The definition is found in the CIOMS Working Group XI report in section 5.3.1, footnote i. The definition was provided by the WHO Global Observatory for eHealth (GOe) for the purposes of the second global survey on eHealth, conducted in 2009.}

176. Minimal risk

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

{A situation where} The probability, and the potential seriousness, of harm or discomfort anticipated in the research are no more than ordinarily encountered in daily life or the performance of routine physical or psychological examinations or tests.

Modified from: Federal Policy for the Protection of Human Subjects, U.S. FDA. (Website, content current as of 24 April 2019)

177. Missing data

CIOMS XIII: Real-world data 2024

Missing data are defined as values that are not available and that would be meaningful for analysis if they were available.

Modified from: Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. New England Journal of Medicine. 2012;4;367(14):1355-1360. https://doi:10.1056/NEJMsr1203730

178. Missing information

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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).

Source: 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 5, 26 July 2024)}

{The EU GVP Annex I 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."}

Earlier/other definition(s):

Missing information

CIOMS VII: DSUR 2006

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.

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

179. Model for end-stage liver disease (MELD)

CIOMS DILI 2020

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.

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

180. Monitoring committee

{See Independent data monitoring committee (IDMC)}

181. Multidisciplinary safety management team (SMT)

CIOMS VII: DSUR 2006

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.

182. Multi-item gamma Poisson shrinkage (MGPS)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Empirical Bayesian algorithm used for signal detection in spontaneous report databases.

Proposed by CIOMS Working Group VIII.

183. Multiplicity

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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

184. Natural history study

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A study that follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease. A natural history study collects health information in order to understand how the medical condition or disease develops and how to treat it.

Source: National Institutes of Health, National Cancer Institute Dictionary of Cancer Terms. (Webpage accessed 15 July 2022)

185. Negative predictive value (NPV)

CIOMS DILI 2020

The proportion of those who tested negative who actually do not have a disease or condition.

Source: 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)

186. Non-interventional study

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A study is non-interventional if it is:

i. Carried out in a database or other form of secondary data; or is
ii. A review of records where all the events of interest have already occurred; or
iii. When all the following conditions are met:
   - The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
   - The assignment of the patient to a particular 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; and
   - No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Interviews, questionnaires, taking of blood samples and patient follow-up may be performed as part of normal clinical practice.

Modified from: European Medicines Agency Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3), 9 October 2017; page 4. (PDF)

{Note: The EU GVP Annex I on definitions (Rev 5, 26 July 2024) refers to the EU Questions & Answers Document on the Clinical Trials Regulation (EU) 536/2014 (Question 1.7) for a description of the difference between non-interventional studies and interventional trials.}

Earlier/other definition(s):

Non-interventional clinical trial, see also Interventional clinical trial

CIOMS VII: DSUR 2006

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.

Source: 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.

187. Non-randomised study

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A study in which the allocation of treatment is **not** decided by chance. Single-arm clinical trials and observational studies are examples of non-randomised studies.

Proposed by CIOMS Working Group XI.

188. Normal clinical practice, see also Current practice

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Medical care typically used in a particular country, region or hospital to treat, prevent, or diagnose a disease or a disorder.

Modified from: European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Article 2(2)(6) (PDF)

189. Null hypothesis

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

190. Number needed to harm (NNH)

CIOMS DILI 2020

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, on average, 25 people would need to be treated for one year for one person to experience a harmful event (1 in 25 people =4%).

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

Earlier/other definition(s):

Number needed to harm (NNH)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

191. Number needed to treat (NNT)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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

192. Odds ratio

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: CIOMS DILI 2020

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.

Earlier/other definition(s):

Odds ratio

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

193. Off-label use

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Use of a medicine or vaccine in a way that is not in line with its authorised use.

Proposed by CIOMS Working Group XI.

Note: Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.

(Antonym: Medicine or vaccine use within label, *i.e.* On-label use)

194. One-sided vs Two-sided testing

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

195. Ongoing clinical trial

CIOMS VII: DSUR 2006

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.

196. On-treatment exposure

CIOMS XIII: Real-world data 2024

The on-treatment exposure definition follows patients from the start until the end of their treatment.

Proposed by the CIOMS Working Group XIII. Based on: Schneeweiss S, Patorno E. Conducting real-world evidence studies on the clinical outcomes of diabetes treatments. Endocrine Reviews. 2021;42(5):658-690. https://doi.org/10.1210/endrev/bnab007

{See also: As-started exposure, Time-varying exposure}

197. Open [data]

Clinical research in RLS 2021

Open means anyone can freely access, use, modify, and share for any purpose (subject, at most, to requirements that preserve provenance and openness).

Source: http://opendefinition.org/. Webpage accessed 3 April 2023.

{The definition is found in section 5.2.1 of the CIOMS Working Group report, see footnote 19.}

198. Outbreak

{See Disease outbreak}

199. Outcome

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

Synonym for Endpoint. See also Composite endpoint.

Proposed by CIOMS Working Group X.

200. Outcome indicators

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: 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, 26 July 2024), as they now see e.g. knowledge and behaviour change also as outcomes of risk minimisation measures.}

201. Over–the–counter (OTC) drug / medicine

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Medicinal product available to the public without prescription.

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

{This glossary is no longer available online.}

Earlier / other definitions:

Non-prescription medicinal products

CIOMS XII: Benefit-risk balance 2025

In this report, non-prescription medicinal products refer to over-the-counter products that have typically transitioned from prescription products to non-prescription products. This excludes e.g. vitamins, supplements and the traditional food industry.

Proposed by CIOMS Working Group XII.

{The definition is found in Section 1.6 of the CIOMS Working Group report, see footnote i.}

P

202. Package leaflet, also called 'Patient product information' *{See also Product information}*

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Adopted by: **MedDRA Labeling Grouping 2024**

A leaflet containing information for the user, which accompanies the medicinal product.

Source: European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 4). 9 October 2017. (PDF)

{Unchanged in the EU GVP Annex I (Rev 5, 26 July 2024).}

Earlier/other definition(s):

Package leaflet

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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).

203. Parametric

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

204. Partial dechallenge / Partial rechallenge

{See Dechallenge / Rechallenge}

205. Passive surveillance (of spontaneous reports)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**

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.

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

206. Patient

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A person who has, or had, a health condition whether or not they currently receive therapy to prevent or treat it.

Modified from: National Health Council. Glossary of patient engagement terms. 13 February 2019. (Webpage)

Earlier/other definitions:

Patient

CIOMS XII: Benefit-risk balance 2025

A person who has, or had, or is at risk of a health condition whether or not they currently receive therapy to prevent or treat it. Patients are the individuals who directly experience the benefits and harms associated with a medicinal product.

Proposed by CIOMS Working Group XII; combined from:
CIOMS XI: Patient involvement 2022
US FDA. Patient-Focused Drug Development Glossary (Webpage accessed 18 July 2024).

{The definition is found in the Foreword to the CIOMS Working Group report, see footnote iii.}

207. Patient-centred outcome

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Outcomes the population of interest notices and cares about (*e.g.* survival, functioning, symptoms, health-related quality of life) and that inform an identified health decision.

Source: Patient-Centered Outcomes Research Institute (PCORI). PCORI Methodology Standards. (Webpage accessed 29 January 2022)

208. Patient community

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Patient community: broadly encompasses individual patients, family caregivers, and the organizations that represent them. The patient community is heterogeneous and brings to the discussion different perspectives informed by their experiences, trajectory or stage of disease, level of expertise, and many other personal, community, and societal factors.

Source: The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem. June 2019. Washington, DC. (PDF)

209. Patient engagement, synonym: Patient involvement

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The active, non-tokenistic and collaborative interaction between patients, the patient community and other stakeholders, where decision making is guided by patients' contributions as partners, recognising their unique experiences, values and expertise.

Modified from: Harrington RL, Hanna ML, Oehrlein EM, Camp R, Wheeler R, Cooblall C, *et al*. Defining Patient Engagement in Research: Results of a Systematic Review and Analysis: Report of the ISPOR Patient-Centered Special Interest Group. *Value Health*. 2020 Jun;23(6):677-688. doi: 10.1016/j.jval.2020.01.019

210. Patient expert

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A person living with a health condition whose knowledge and experience enables the person to take more control over personal health by understanding and managing the health condition.

Expert patients may also act as advocates for their condition and help other patients with the same health issue.

Proposed by CIOMS Working Group XI.

211. Patient-focused drug development (PFDD)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A systematic approach to capture patients' experiences, perspectives, needs and priorities, and to incorporate them meaningfully into the development and evaluation of a medicinal product throughout its lifecycle.

Modified from: U.S. Food and Drug Administration. Patient-Focused Drug Development Glossary. (Webpage, content current as of 8 June2018)

212. Patient group

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Patient organisation

213. Patient information leaflet (PIL)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Package leaflet

214. Patient labelling

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Package leaflet

215. Patient ombudsman

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A neutral person (or body) responsible for receiving, investigating and responding to patients' complaints on health services or other support services provided to patients.

Modified and combined from:
- Patient Ombudsman. Vision, Mission, and Values. Toronto, Ontario, Canada. (Webpage accessed 14 December 2021)
- Parliamentary and Health Service Ombudsman, UK. (Webpage accessed 14 December 2021)

216. Patient organisation, synonym: Patient group

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An institution that represents the interests and needs of patients (and their families and caregivers) who have a particular disease, disability or group of diseases and disabilities. Patient organisations may engage in research, education, advocacy and fundraising to further the needs of their patient group.

Proposed by CIOMS Working Group XI.

217. Patient Package Insert (PPI)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Package Leaflet

218. Patient preference

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

See Patient preference studies

219. Patient preference elicitation methods

CIOMS XII: Benefit-risk balance 2025

Preference elicitation methods refer to quantitative methods collecting quantifiable data for hypothesis testing and other statistical analyses used to measure patient preference information. These methods provide among others information about which benefits and risks are most important to patients or what maximal level of risk (known as maximum acceptable risk) patients are willing to accept for a given level of benefit.

Proposed by CIOMS Working Group XII.

Commentary: These methods can be grouped in four categories:[1]

- discrete choice-based methods typically examine the importance of trade-offs between attributes and their alternatives through a series of choice sets that present (hypothetical) alternatives;
- ranking (or related) methods compare multiple pairs of attributes or alternatives where one of the two options is selected for each pairing presented – the selections are aggregated to yield an overall ranking of the proposed options;
- indifference techniques are methods that vary the value of one attribute in one of the alternatives until the participant is indifferent, or has no preference, between alternatives;
- rating (or related) methods usually allow participants to express the strength of their preferences along a labelled scale after which these ratings are compared.

[1] Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discovery Today. 2019;1;24(7):1324-1331. https://doi.org/10.1016/j.drudis.2019.05.001

{The definition is found at the start of Section 3.3.2 of the CIOMS Working Group report.}

220. Patient preference information

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Patient preference information is defined as information resulting from 'assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions'[1]. Patient preference information can be determined through qualitative and quantitative methods, and includes the relative importance of what matters most

to patients, enabling the examination of trade-offs that patients are willing to make between benefits and harms.[2]

[1] U.S. Food and Drug Administration (FDA) Patient-Focused Drug Development Glossary. https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary

[2] Mühlbacher A, Bethge S. What matters in type 2 diabetes mellitus oral treatment? A discrete choice experiment to evaluate patient preferences. Eur J Health Econ 2016; 17: 1125–1140. https://doi.org/10.1007/s10198-015-0750-5

{The definition is found in the last paragraph on page 77 of the CIOMS Working Group report.}

221. Patient preference studies

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The qualitative or quantitative assessment of the desirability, or acceptability to patients of choices of outcomes or other attributes, that differ among alternative health interventions.

Modified and combined from:
– U.S. Food and Drug Administration. Advancing Use of Patient Preference Information as Scientific Evidence in Medical Product Evaluation, Collaborative Workshop hosted by Centers of Excellence in Regulatory Science and Innovation (CERSIs) and the Food and Drug Administration. December 7-8, 2017. (Webpage, content current as of 29 March 2018)
– U.S. Food and Drug Administration. Patient Preference-Sensitive Areas: Using Patient Preference Information in Medical Device Evaluation. (Webpage, content current as of 29 September 2020)

222. Patient registry

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An organised system that collects uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Modified from: European Medicines Agency Guideline on good pharmacovigilance practices (GVP). Annex I - Definitions (Rev 4). (PDF)

{The EU GVP Annex I (Rev 5, 26 July 2024) has adopted the definition from the 2021 EMA Committee for Human Medicinal Products (CHMP) Guideline on Registry-based studies, which is similar to that shown above (differences in bold): "…collect uniform data ***(clinical or other) to identify*** *specified outcomes* ***for*** *a population…".}*

{See also: Registry}

223. Patient-reported outcome

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Data reported directly by the patient about aspects of their health without prior interpretation of the patient's response by a clinician or anyone else.

Modified from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. Glossary. 2016 Jan 28 [Updated 2021 Nov 29]. (Webpage)

Earlier/other definition(s):

Patient-reported outcome (PRO)

CIOMS XIII: Real-world data 2024

A measurement of any aspect of a patient's health status that comes directly from the patient without the interpretation of the patient's responses by a physician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response.

Modified from: U.S. Department of Health and Human Services, Food and Drug Administration (FDA). Guidance for Industry Patient Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims. 2009. (PDF)

{See also: Economic outcomes, Surrogate outcomes)

{This is shown as an "Other definition" here because the Working Group XIII report does not have a formal glossary, nor does it focus on patient-related topics.}

224. Patient safety organisation

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A group, institution, or association that improves patient care by reducing medical risks and hazards.

Modified from: Agency for Healthcare Research and Quality. Guide to Improving Patient Safety in Primary Care Settings by Engaging Patients and Families. Appendix E: Category Definitions. Content last reviewed March 2017. (Webpage)

225. Patient voice

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The input and perspective of patients on their needs and what is of value to them, which can differ from needs identified by other stakeholders (*e.g.* medicine developers, physicians, regulators, and payers).

Modified from: National Health Council (NHC). *The patient voice in value: the NHC patient-centered value model rubric*. March 2016. (PDF)

226. Payer

CIOMS XIII: Real-world data 2024

In healthcare, a payer is a person, organisation, or entity that pays for the care services provided by a health care professional (HCP). It most often refers to government or private insurance companies, which provide customers with health

plans that offer cost coverage and reimbursements for medical treatment and care services.

Proposed by CIOMS Working Group XIII.

227. Periodic safety update report (PSUR)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

{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 5, 26 July 2024).

In the EU GVP Annex I the definition is followed by a note: "In the EU, periodic safety update reports should follow the format described in GVP Module VII".}

228. Pharmaceutical industry

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

(See Industry, pharmaceutical)

229. Pharmacoepidemiology, see also Pharmacology and Epidemiology

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The study of the use and effects of drugs (including biologicals and vaccines) in large* numbers of people using methods, analyses and reasoning based on general epidemiology.

* 'Large' is dependent on the study and the disease.

Modified from: International Society of Pharmacoepidemiology. About Pharmacoepidemiology. (Webpage accessed 10 December 2021)

Earlier/other definition(s):

Pharmacoepidemiology

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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: Signal detection 2010 | (Chinese translation available, see page xii)

Study of the use and effects of drugs in large populations.

Source: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. (Webpage)

{This glossary is no longer available online.}

230. Pharmacogenomics, pharmacogenetics

Clinical research in RLS 2021

The ICH E15 guideline includes the following definitions: **Pharmacogenomics (PGx):** The study of variations of DNA and RNA characteristics as related to drug response. **Pharmacogenetics (PGt)** is a subset of pharmacogenomics (PGx) and is defined as: The study of variations in DNA sequence as related to drug response.[313] In practice the two definitions are often used interchangeably.

Reference 313: ICH Harmonised Tripartite Guideline. Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data And Sample Coding Categories. E15. Current Step 4 version dated 1 November 2007. (PDF)

Proposed by the CIOMS Working Group on Clinical Research in RLS.

{The definition is found in Appendix 5 of the CIOMS Working Group report, see footnote 25.}

231. Pharmacology

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The scientific study of the properties of drugs and their effects on the body.

Modified from: Oxford concise medical dictionary, 8th edition, 2010. (Online dictionary accessed 17 January 2022)

{As at 15 July 2022, the definition at the above-mentioned online dictionary link reads: "the science of the properties of drugs and their effects on the body".}

232. Pharmacovigilance

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by:
- CIOMS VII: DSUR 2006
- CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)
- CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)
- CIOMS DILI 2020
- MedDRA Labeling Grouping 2024

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

{Although the definition is the same in the CIOMS reports listed above, different sources are cited, and the two earliest groups added a commentary. See details below.}

CIOMS VI: Clinical trial safety information 2005

Source: 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.

CIOMS VII: DSUR 2006

{Same source as in CIOMS VI above}.

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.

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Source: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. (http://www.who-umc.org/graphics/8321.pdf, accessed 11 December 2009). *{This PDF file is no longer available online.}*

CIOMS DILI 2020

Source: The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva, WHO, 2002. **(**PDF**)**

MedDRA Labeling Grouping 2024

Source: WHO. Pharmacovigilance strategies [webpage]. Accessed 31 January 2024.

233. Pharmacovigilance system

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: 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 5, 26 July 2024).}

{In the EU GVP Annex I 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)]."}

234. Phases of clinical studies (I-IV)

CIOMS VII: DSUR 2006

- 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.

Source: 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.).

Earlier/other definition(s):

Phases of clinical studies (I – IV)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

- 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.

Source: 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.).

235. Plain language

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Communication that the audience can understand the first time they read or hear it.

Modified from: plainlanguage.gov. What is plain language? (Webpage accessed 14 December 2021)

236. Point estimate

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

237. Poisson distribution

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

238. Positive predictive value (PPV)

CIOMS DILI 2020

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

Source: 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)

239. Post-authorization

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

{See also Post-marketing; Pre-marketing}

240. Post-authorisation efficacy study (PAES)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A study conducted after a medicine is authorised to address scientific uncertainties around how well a medicine works in its authorised indication.

Note. For a medicine to be authorised, the benefit risk balance must be positive. PAES are required when there is some uncertainty on the level of the benefit that can only be addressed after the medicine is authorised, or when there is new information suggesting that previous assumptions may need to be revised.

Proposed by CIOMS Working Group XI (based on Scientific guidance on post-authorisation efficacy studies. EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)

241. Post-authorisation safety study (PASS)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [DIR 2001/83/EC Art 1(15)].

A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.

Source: European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 4). 9 October 2017. (PDF)

{Unchanged in the EU GVP Annex I (Rev 5, 26 July 2024).

Earlier/other definition(s):

Post-authorisation safety study (PASS)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

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

{In the EU GVP Annex I 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."}

242. Post-marketing

CIOMS DILI 2020

The stage when a drug is approved and generally available on the market.

Source: Uppsala Monitoring Centre (UMC). Glossary of pharmacovigilance terms (Webpage, accessed 29 March 2020) *{Link no longer current as at 15 July 2022.}*

{See also: Post-authorization, Pre- marketing}

Earlier/other definition(s):

Post-marketing

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

The stage when a drug is available on the market.

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

{This glossary is no longer available online.}

243. Post-marketing surveillance

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Monitoring for adverse reactions to marketed products.

Modified from: Glossary of MHRA terms. (Webpage, accessed 11 December 2009)

244. Potential risk

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: CIOMS SCAR 2025 (without the examples)

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.

Source: 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 5, 26 July 2024), as well as the ICH E2F Guideline: Development Safety Update Report (17 August 2010). In both these documents some of the examples are worded slightly differently than in the CIOMS IX definition.}

Earlier/other definition(s):

Potential risk

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: Guideline on Risk Management Systems for medicinal products for human use, Volume 9A of Eudralex, Chapter I.3., March 2007.
https://ec.europa.eu/growth/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf

{Link no longer valid as of July 2022. Definition maintained in: Eudralex Volume 9A. Rules Governing Medicinal Products in the European Union. Guidelines on Pharmacovigilance for Medicinal Products for Human Use. September 2008. Chapter I.3. (PDF)}

Potential risk

CIOMS VII: DSUR 2006

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.

Source: 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.

245. Power

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

246. Pragmatic trial

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A randomised controlled study designed to evaluate the effectiveness of interventions in real-life routine practice conditions.

Modified from: Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011;13(2):217-24. doi: 10.31887/DCNS.2011.13.2/npatsopoulos

247. Preference elicitation methods

{See Patient preference elicitation methods}

248. Pre-marketing, synonym: Pre-authorization

CIOMS DILI 2020

The developmental stage before a drug is approved and available for prescription or sale to the public.

Source: Uppsala Monitoring Centre (UMC). Glossary of pharmacovigilance terms (Webpage, accessed 29 March 2020) *{Link no longer current as at 15 July 2022.}*

{See also Post-authorization; Post-marketing}

Earlier/other definition(s):

Pre-authorization

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

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

{Link no longer current as of 15 July 2022. Definition not found in ICH harmonized guideline on General considerations for clinical studies, E8(R1).}

Pre-marketing

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

The stage before a drug is available for prescription or sale to the public. Usually synonymous with pre-approval or pre-authorization.

Source: Glossary of terms used in Pharmacovigilance, WHO Collaborating Centre for International Drug Monitoring, Uppsala. *{This glossary is no longer available online.}*

249. Prescription event monitoring (PEM) or Cohort event monitoring (CEM)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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”.

Source: Glossary of terms used in Pharmacovigilance. WHO Collaborating Centre for International Drug Monitoring, Uppsala. *{This glossary is no longer available online.}*

250. Prevalence

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Number of existing cases of an outcome or disease in a defined population at a given point in time. Prevalence is calculated as a proportion (cases divided by the total defined population) and is often expressed as a percentage, or as the number of cases per 10,000 or 100,000 people.

Modified from: CIOMS Working group report on Drug-induced liver injury (DILI). 2020.

Note: Prevalence should be distinguished from Incidence, see CDC Web Archive*: 'Prevalence and incidence are frequently confused. Prevalence refers to proportion of persons who have a condition at or during a particular time period, whereas incidence refers to the proportion or rate of persons who develop a condition during a particular time period.'

* Centres for Disease Control (CDC). Principles of Epidemiology in Public Health Practice, Third Edition. An Introduction to Applied Epidemiology and Biostatistics. Lesson 3: Measures of Risk, under 'Properties and uses of prevalence'. (Webpage accessed 9 February 2022).

Earlier/other definition(s):

Prevalence

CIOMS DILI 2020

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.

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

{Link no longer current as at 15 July 2022.}

Prevalence

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Rothman KJ, Green land S, Lash T. Modern Epidemiology.3rd edition. Lippincott Williams & Wilkins. 2008:46.

251. Primary endpoint

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

252. Privacy (in relation to processing personal data)

CIOMS XIII: Real-world data 2024

The individual citizen has human rights, particularly privacy rights in relation to the processing of their personal data. These are expressed primarily in duties imposed on those who process personal data (or who have obligations flowing from someone with such duties), and actionable rights on the part of the individuals themselves to whom the data relate (data subjects).

Combined and modified from:

Council of Europe (1981) The Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data CETS No. 108 (PDF)

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (EUR-Lex Webpage accessed 10 May 2024)

253. Process indicators

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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, 26 July 2024), as they now see e.g. knowledge and behaviour change also as outcomes of risk minimisation measures.}

254. Product information (PI)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**
MedDRA Labeling Grouping 2024

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. The EU labelling on the immediate or outer packaging is a part of product information.

{Figure 1.1: see next page}

Figure 1.1: Examples of nomenclature for components of product information

PRODUCT INFORMATION (PI)	
Product information for HCPs* • Summary of product characteristics (SmPC, also sometimes SPC) • Data sheet • Drug data sheet • Safety data sheet • Package insert • Product information	Product information for patients • 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} {see also Package leaflet}*

Proposed by CIOMS Working Group IX.

255. Proportional reporting ratio (PRR)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

256. Proteomics

CIOMS DILI 2020

The study of the structure and function of proteins, including the way they work and interact with each other inside cells.

Source: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage accessed March 2020)

257. Protocol-related adverse event

CIOMS VII: DSUR 2006

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

258. Qualification

CIOMS DILI 2020

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.

Source: 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)

259. Qualitative research methods

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Methods associated with the gathering, analysis, interpretation, and presentation of narrative information (e.g. spoken or written accounts of experiences, observations, and events). Qualitative research methods may also include direct observations (e.g. non-verbal communication and behaviours).

Source: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input, Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Department of Health and Human Services Food and Drug Administration. June 2020. (PDF)

260. Qualitative signal detection

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

261. Quantitative research methods

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Methods associated with the gathering, analysis, interpretation, and presentation of numerical information.

Source: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input, Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Department of Health and Human Services Food and Drug Administration. June 2020. (PDF)

262. Quantitative signal detection

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

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

R

263. Random effects

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

264. Rank

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

265. Reach

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: 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.

266. Real-world data (RWD)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Health care data gathered from routine clinical practice in a non-interventional setting. RWD can come from wide variety of sources such as electronic claims and health records, registries, patient reported outcomes, digital tools/mobile devices. Data collected include clinical and economic outcomes, patient-reported outcomes (such as disease activity and quality of life) and resource utilisation.

Source: Report of CIOMS Working Group XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making (work in progress at the time of publishing the CIOMS XI report on Patient involvement).
Published in June 2024, available at: https://doi.org/10.56759/kfxh6213

Note:

CIOMS XIII: Real-world data 2024

{The CIOMS Working Group XIII report does not propose a definition of RWD. It states: "Although various definitions of RWD have been proposed (see Table 1 for examples), there is currently no consensus definition." It goes on to say: "These definitions of RWD are largely overlapping and similar in their essence. Given these and other existing definitions of this evolving field, the WG declined to put forth yet another definition."}

Earlier/other definition(s):

Real-world data (RWD)

CIOMS DILI 2020

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.

Source: 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)

267. Real-world evidence

CIOMS XIII: Real-world data 2024

Real-world evidence (RWE) is evidence derived from the review and/or analysis of real-world data (RWD).

Modified from: Zuidgeest MGP, Goetz I, Meinecke AK, et al. The GetReal Trial Tool: design, assess and discuss clinical drug trials in light of Real World Evidence generation. J Clin Epidemiol. 2022 Sep;149:244-253. doi: 10.1016/j.jclinepi.2021.12.019

Earlier/other definition(s):

Real-world evidence

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The evidence derived from the review and analysis of Real-world data.

Adopted from: Report of CIOMS Working Group XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making (work in progress at the time of publishing the CIOMS XI report on Patient involvement).
Published in June 2024, available at: https://doi.org/10.56759/kfxh6213}

268. Receiver-operating characteristic (ROC) curve

CIOMS DILI 2020

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.

Source: JAMAevidence® Glossary. (Webpage accessed 29 March 2020)

269. Rechallenge

{See Dechallenge / Rechallenge}

270. Reference risk (baseline risk)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

271. Registry

CIOMS DILI 2020

(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.

Source: 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.

Source: 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.

{See also: Patient registry}

Earlier/other definition(s):

Registry

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

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

Registry

CIOMS VII: DSUR 2006

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.

Source: 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.

272. Regression

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

273. Regulator, medicines (synonyms: Regulatory authority, Health authority)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A legally mandated body concerned with ensuring the quality, safety, efficacy, manufacture, sale or marketing of medicines including biologicals and vaccines.

Medical regulators can be regional, national (for example FDA, PMDA or MHRA), or supranational (for example EMA).

Proposed by CIOMS Working Group XI.

274. Relative risk

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Earlier/other definition(s):

Relative risk (RR)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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: Benefit-risk 1998

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.

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

275. Reporting odds ratio (ROR)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

276. Research organisation

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A body that performs one or more activities in relation to the development of medicines or other treatments, or for investigating the causes, prevention, progression and treatment of diseases.

A research organisation may be academic, not-for-profit or for-profit. It may perform research for itself or on behalf of another organisation.

Proposed by CIOMS Working Group XI.

277. Resource-limited setting (RLS)

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A country or locale where the capability to provide care for life-threatening illness to most of the population is limited to basic critical care resources, with no or very limited possibility of referral to higher care capability.

Modified from: Geiling J, Burkle FM Jr, Amundson D, *et al.* Resource-poor settings: infrastructure and capacity building: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest.* 2014;146(4 Suppl):e156S-167S. doi: 10.1378/chest.14-0744

278. Restricted access programme, also known as Managed/Controlled access in some jurisdictions

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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 Feb 2014).

{Examples maintained in subsequent version, Module XVI (Rev 2, 28 March 2017); see page 8), but not in Module XVI, (Rev 3, 26 July 2024), where revised guidance on risk minimisation control tools and programmes has replaced draft guidance on controlled access programmes.

279. Risk

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The probability of an adverse event, or an outcome, in a defined population over a specified time interval.

Modified from: A dictionary of Epidemiology. 6th edition. Miquel Porta (editor). Oxford University Press; 2014. (Online dictionary accessed 8 February 2022)

Earlier/other definition(s):

Risk

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)
Adopted by: **CIOMS SCAR 2025**

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: Signal detection 2010 | (Chinese translation available, see page xii)

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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)
{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: Benefit-risk 1998

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.

280. Risk assessment

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: FDA Guidance for Industry. Premarketing Risk Assessment. March 2005.

Earlier/other definition(s):

Risk assessment

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: 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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: Risk analysis, perception and management. The Royal Society UK, 1992

281. Risk avoidance

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

An informed decision not to become involved in activities that lead to the possibility of the risk being realized.

Source: Risk Management and Decision Making Glossary.
http://www.argospress.com/Resources/risk-management/ *{This webpage is no longer online}*

282. Risk-benefit balance

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: 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 5, 26 July 2024).}

283. Risk communication

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Decision-making framework for identifying, assessing and managing health risks, Health Canada, 1 August 2000. (PDF)

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.

Earlier/other definition(s):

Risk communication

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: 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.

284. Risk difference

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

The difference between two proportions. For more detail, refer to the original definition.

Proposed by CIOMS Working Group X.

285. Risk elimination

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

'Absolute' or complete prevention of risk, *i.e.* reduction of the frequency of an undesirable outcome to zero.

Proposed by CIOMS Working Group IX.

286. Risk estimation

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Source: Risk analysis, perception and management, The Royal Society, UK. 1992.

287. Risk evaluation

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

Source: Risk analysis, perception and management, The Royal Society, UK. 1992.

Earlier/other definition(s):

Risk evaluation

CIOMS IV: Benefit-risk 1998

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.

288. Risk evaluation and mitigation strategy (REMS)

CIOMS DILI 2020

A drug safety program 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.

Source: U.S. FDA website. Risk Evaluation and Mitigation Strategies (REMS). Updated 8 August 2019. (Webpage)

{Definition maintained on the above-mentioned webpage having content current as of 17 December 2021.}

Earlier/other definition(s):

REMS (Risk evaluation and mitigation strategy)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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. 'Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications'. 2009 (PDF)

{In July 2022, the PDF posted at the above link was a revised version of the draft FDA guidance: Format and Content of a REMS Document. Guidance for Industry. October 2017.}

289. Risk factor

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: CIOMS DILI 2020

Characteristics associated with an increased probability of occurrence of an event or disease.

Source: Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

290. Risk identification

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Determining what risks or hazards exist or are anticipated, their characteristics, remoteness in time, duration period, and possible outcomes.

Source: http://www.businessdictionary.com/definition/risk-identification.html, accessed 16 June 2013.

{Link no longer current as of May 2021. Definition found at this link: https://www.w3definitions.com/risk-identification/, 15 July 2022}

291. Risk level / Level of risk

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Characterisation of an undesirable outcome by severity and likelihood of occurrence.

Proposed by CIOMS Working Group IX.

292. Risk management

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

Earlier/other definition(s):

Risk management

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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: Benefit-risk 1998

The making of decisions concerning risks, or action to reduce the consequences or probability of occurrence.

Source: Risk: Analysis, Perception and Management. Report of a Royal Society Study Group. The Royal Society. London, 1992.

293. Risk management plan (RMP)

CIOMS DILI 2020

(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)].

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.)

{The EU GVP definition remained unchanged in Annex I - Definitions (Revision 5, 26 July 2024).}

Earlier/other definition(s):

Risk management plan (RMP)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

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

294. Risk management system

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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)].

Source: 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 5, 26 July 2024), except that the definition refers to risks relating to "a medicinal product" in the singular.}

Earlier/other definition(s):

Risk management system

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

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

295. Risk minimization

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: CIOMS DILI 2020

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.

296. Risk minimisation action plans (RiskMAPs)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.}

297. Risk minimisation-burden balance

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

298. Risk minimisation exposure

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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. Implement Sci. 2007;2:40. Published 2007 Nov 30. doi:10.1186/1748-5908-2-40

299. Risk minimisation measure, synonym: Risk minimisation activity; see also Additional risk minimisation measure and Routine risk minimisation measure

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An intervention (or series of interventions) intended to prevent, reduce the occurrence, or reduce the severity, of an undesirable outcome associated with the use of a medicine (adverse reaction). Risk minimisation measures may be routine or additional.

Modified from: CIOMS Working Group IX, glossary definition of 'Routine risk minimisation activity'. The CIOMS WG IX definition was originally modified from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

Earlier/other definition(s):

Risk minimisation intervention / Risk minimisation activity / Risk minimisation measure (synonyms)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

300. Risk minimisation plan

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

301. Risk minimisation programme

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

A system of risk minimisation action(s) that are described and derived from a risk minimisation plan.

Proposed by CIOMS Working Group IX.

302. Risk minimisation strategy

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

303. Risk minimisation target

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Recipient or audience for a risk minimisation intervention instrumental to its implementation, *e.g.* healthcare providers.

Proposed by CIOMS Working Group IX.

304. Risk minimisation tool

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

305. Risk mitigation

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**

Reduction of the severity of an undesirable outcome should it occur.

Proposed by CIOMS Working Group IX.

306. Risk prevention

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**

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.

307. Risk ratio

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

308. Risks related to use of a medicinal product

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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)].

Source: 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 5, 26 July 2024).}

309. Routine pharmacovigilance

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The set of pharmacovigilance activities required by a regulatory authority for every medicinal product they authorise.

In many regions, these minimum requirements are laid down in law or regulations.

Proposed by CIOMS Working Group XI.

Earlier/other definition(s):

Routine pharmacovigilance

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

310. Routine risk minimisation measure, synonym: Routine risk minimisation activity; see also Additional risk minimisation measure and Risk minimisation measure

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

A risk minimisation measure which is mandatory for all medicinal products in a particular region or territory. Routine risk minimisation measures typically include

standard activities such as product labelling, limitations on drug pack size and the legal status of the product.

Modified from: CIOMS Working Group IX, glossary definition of 'Routine risk minimisation activity'. The CIOMS WG IX definition was originally modified from: EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

Note: The legal status of a product relates to whether the medicine must be prescribed by a doctor, whether it can be bought from a pharmacist without a prescription, or whether it can be on general sale in a shop.

Earlier/other definition(s):

Routine risk minimisation activities

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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).

S

311. Safety concern

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

An important identified risk, important potential risk or missing information.

Source: 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 5, 26 July 2024).}

312. Safety profile

CIOMS Glossary Advisory Board, June 2024

The overall concise and accurate summary of the most serious and frequently occurring adverse reactions for a given medicinal product at a given point in time. Knowledge about a medicinal product's safety profile evolves as safety-related data accumulates over time from a variety of sources. A safety profile can also include information about the lack of an adverse or other effect when it has not been observed in the exposed population, or a particular subsection of the exposed population, during the course of treatment.

Proposed by the CIOMS Cumulative Glossary Advisory Board, June 2024. Based on: European Commission. A guideline on summary of product characteristics (SmPC). September 2009. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

313. Safety-related outcome of interest, see also Outcome indicators

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

314. Scatterplots

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

315. Sensitivity

CIOMS DILI 2020

The proportion of people with a positive test result among those with the target condition.

Source: JAMAevidence® Glossary. (Webpage accessed 29 March 2020)

Earlier/other definition(s):

Sensitivity

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

316. Sensitivity analysis

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Source: Glossary of Terms in the Cochrane Collaboration. Version 4.2.5, May 2005. (PDF)

317. Sequential meta-analysis

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

318. Serious

CIOMS IV: Benefit-risk 1998

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):[1]

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.

[1] 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.

{Not synonymous with: Severe}

{See also Serious adverse event, Serious adverse reaction}

Earlier/other definition(s):

Serious

CIOMS II: PSUR 1992

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.

319. Serious adverse event

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Adopted by: **CIOMS SCAR 2025** (in-text, with slightly different wording also including the words "at any dose", as in the CIOMS IX definition shown below under "Earlier/other definitions")

Any untoward medical occurrence that:

- results in death;
- is life-threatening;
- requires hospitalisation or results in prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- is a medically important event or reaction.

Modified from: ICH harmonised tripartite guideline. Post-approval safety data management: Definitions and standards for expedited reporting. E2D. 12 November 2003. (PDF)

Note: In pharmacovigilance, the term "event" is used when it is not known or suspected that the occurrence or effect was caused by the medicine.

{See also: Serious, Serious adverse reaction, Adverse event, Adverse drug reaction}

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

Earlier/other definition(s):

Serious adverse event

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

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

320. Serious adverse reaction, see also Adverse reaction

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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)].

Source: 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 5, 26 July 2024). The definition in the GVP Annex I is followed by these notes:
"Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see GVP Annex IV, ICH-E2D Guideline).
Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. 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 dependency or abuse (see Annex GVP Annex IV, ICH-E2D Guideline).
Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction."}

{See also Serious, Serious adverse event}

Earlier/other definition(s):

Serious adverse reaction/Adverse drug reaction

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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: DSUR 2006

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.

Source: 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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

Source: 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.

321. Severe/Severity

CIOMS IV: Benefit-risk 1998

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.

{See also: Serious}

322. Shared decision making

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

In medicine, a process in which both the patient and healthcare professional work together to decide the best plan of care for the patient. When making a shared decision, the patient's values, goals, and concerns are considered.

Source: National Cancer Institute. NCI Dictionary of Cancer Terms. (Webpage accessed 23 February 2022)

323. Signal

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: **CIOMS DILI 2020**

{Note: In the DILI WG report the last clause, '…that is judged to be of sufficient likelihood to justify verificatory action', was omitted. This was done inadvertently, not as a result of a consensus.}

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)

Earlier/other definition(s):

Signal

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)
Adopted by: MedDRA Labeling Grouping 2024

Information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Source: Uppsala Monitoring Centre (UMC). What is a signal? (Webpage accessed 9 February 2022)

Signal

CIOMS VII: DSUR 2006

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.

Source: 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: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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: Benefit-risk 1998

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.

Source: Hartzema, A.G., Porta, M.S. and Tilson, H.H. Pharmacoepidemiology: An Introduction. Harvey, Whitney Books. Cincinnati, Ohio, 1988.

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.

324. Signal detection

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

Adopted by: **CIOMS IX: Risk minimisation 2014** | (Japanese translation available, see page xii)
CIOMS XI: Patient involvement 2022

The act of looking for and/or identifying signals using event data from any source.

Proposed by CIOMS Working Group VIII.

325. Signal management

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

326. Signal, verified

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

327. Significance, Significant, Significantly

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

328. Simes

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

A method similar to a Bonferroni correction (see above) but with greater power.

Proposed by CIOMS Working Group VI.

329. Special populations, see also Vulnerable populations

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Populations to be considered should include (but might not be limited to):

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Source: ICH harmonised tripartite guideline. Pharmacovigilance Planning. E2E. (PDF)

Earlier/other definition(s):

Special populations, see also Vulnerable

Clinical research in RLS 2021

In this report […] the term "special populations" is used to describe populations with physiological characteristics that warrant their being considered separately in clinical research, such as children, pregnant women and the elderly (see Appendix 1). The two categories may overlap.

Proposed by the CIOMS Working Group on Clinical Research in RLS.

{The definition is found in section 4.1 of the CIOMS Working Group report, see footnote 16.}

330. Specificity

CIOMS DILI 2020

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.

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

331. Sponsor

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial or study.

Modified from: CIOMS Working Group IX.

Earlier/other definition(s):

Sponsor

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

Adopted by: **CIOMS VII: DSUR 2006**
CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)
CIOMS DILI 2020

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

{CIOMS VI} **Source: ICH Guideline: E6 Good Clinical Practice.** In the EU: Identical to the above definition.

{CIOMS VIII} **Source: ICH Guideline for Good Clinical Practice E6(R1).**

{CIOMS IX} [Directive 2001/20/EC Art 2(e)]. **Source: Eudralex Volume 9a (Sep 08), Glossary 1.3.**

332. Spontaneous report

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

333. Stakeholder

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Individuals or organisations involved in the development, regulation and safe use of a medicine during its life-cycle. These may include:

- Medicine developers (pharmaceutical and healthcare industry and academia);
- Patients, patient organisations and patient advocates;
- Regulators;
- Health Technology Assessment bodies;
- Payers; and
- Healthcare professionals

Modified from: Innovative Medicines Initiative (IMI), Patients Active in Research and Dialogues for and Improved Generation of Medicines (PARADIGM). *D4.1 Recommendations on the required capabilities for patient engagement*. 2018. (PDF)

334. Standard of care, see also Current Practice and Normal Clinical Practice

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Medical care that is the customary treatment, diagnosis or prevention of a disease or disorder in a particular region or setting. This may be as defined in guidelines issued by a relevant medical body, mandated by regulatory and/or medical authorities or as routinely performed by a reasonable proportion of healthcare professionals.

Proposed by CIOMS Working Group XI

Earlier/other definition(s):

Standard of care

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

335. Standardised MedDRA Query (SMQ)

MedDRA: see more under MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA Labeling Grouping 2024

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded.

Source: Introductory Guide for Standardised MedDRA Queries (SMQs). Version 24.1. September 2021. Available at:
https://admin.meddra.org/sites/default/files/guidance/file/000595_SMQ_intguide_24_1.pdf

{See also the CIOMS Working Group report on Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA. *Report of the CIOMS SMQ Implementation Working Group. Second Edition. Geneva: CIOMS, 2016. Freely available on the CIOMS website.}*

336. Statistic of disproportionate reporting (SDR)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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.

337. Structural alerts

CIOMS DILI 2020

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.

Source: 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)

338. Summary-level data

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

339. Summary of product characteristics (SmPC)

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

{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).

{In the EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5, 26 July 2024), the definition is as follows:
"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)."}

Earlier/other definition(s):

Summary of product characteristics (SmPC)

MedDRA Labeling Grouping 2024

In the European Union, a document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively.

Modified from: European Commission. A guideline on summary of product characteristics (SmPC). September 2009. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

{In the CIOMS report on MedDRA Labeling Grouping the above definition is followed by an extract of the SmPC Section 4.8 titled "Undesirable effects", which is particularly relevant to that report.}

{The definition of the CIOMS IX report on Risk Minimisation (2014) is shown in this glossary as the current one, as it is closer to that included in the EU Guideline on Good pharmacovigilance practice.}

340. Survival analysis

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

341. Surrogate endpoint

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

{See also Surrogate outcomes}

342. Surrogate outcomes

CIOMS XIII: Real-world data 2024

These outcomes are used as substitutes for clinical outcomes, and are thought to predict clinical outcomes. Examples of surrogate outcomes include biomarkers, imaging findings, or laboratory tests considered to be associated with a particular disease or condition.

Proposed by CIOMS Working Group XIII.

{See also: Economic outcomes, Patient-reported outcome; Surrogate endpoint}

343. Survey

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

344. Suspected unexpected serious adverse reactions (SUSAR)

CIOMS VII: DSUR 2006

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]

Source: 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).

Earlier/other definition(s):

Suspected unexpected serious adverse reaction (SUSAR)

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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]

Source: 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.}

345. Systematic error

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

346. Systematic review

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An organised evaluation with the aim of collating all scientific evidence and experience that fits the pre-specified eligibility criteria in order to answer a specific research question.

Modified from: Cochrane Training, Handbook, Chapter 1. (Webpage accessed 14 December 2021)

Earlier/other definition(s):

Systematic review

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

Source: Glossary of Terms in The Cochrane Collaboration. Version 4.2.5, May 2005. (PDF)

T – U

347. Target population

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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 5, 26 July 2024).}

348. Targeted follow-up questionnaire

CIOMS IX: Risk minimisation 2014 | (Japanese translation available, see page xii)

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.

349. Targeted medical event (TME)

CIOMS VIII: Signal detection 2010 | (Chinese translation available, see page xii)

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 (PDF)

350. Telemedicine

CIOMS XI: Patient involvement 2022)

Telemedicine is the provision of healthcare services at a distance with communication conducted between healthcare providers seeking clinical guidance and support from other healthcare providers (provider-to-provider telemedicine); or conducted between remote healthcare users seeking health services and healthcare providers (client-to-provider telemedicine)

Modified from: WHO guideline: recommendations on digital interventions for health system strengthening. Geneva, Switzerland: World Health Organization, 2019. (PDF)

{The definition is included in the CIOMS Working Group XI report in section 5.3.1, footnote i.}

351. Time-varying exposure

CIOMS XIII: Real-world data 2024

In the time-varying exposure definition, patients are followed from a cohort entry point and their exposure status is allowed to vary over time.

Modified from: Suissa S. Immortal time bias in pharmacoepidemiology. American Journal of Epidemiology. 2008;167(4):492-499. https://doi.org/10.1093/aje/kwm324

{See also: On-treatment exposure, As-started exposure}

352. Traditional data sources

CIOMS XIII: Real-world data 2024

The scope of real-world data (RWD) usually includes health care data sources that can provide information that can be used to infer the benefits and risks of medicinal products and measure resource utilisation. While this scope is appropriate, it is incomplete. There are other sources that, although not as rich for capturing information from the provision of health care, are useful for evaluating the safety and effectiveness of products and the burden of diseases in different populations. They include spontaneous reporting systems (SRSs) and surveys. Such sources have been used to evaluate the benefits and risks of products for decades. For the purpose of this document, health care data and other sources mentioned above will be called traditional data sources.

Proposed by CIOMS Working Group XIII

{See also Emerging data sources}

353. Trial

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

354. Tumour-agnostic therapy

CIOMS DILI 2020

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.

Source: United States National Cancer Institute (NCI). NCI Dictionary of cancer terms. (Webpage accessed March 2020)

355. Type I and Type II errors

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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.

356. Unmet medical need

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

An unmet medical need is a condition whose prevention, treatment or diagnosis is not addressed adequately by what is available.

Modified from: U.S. Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014. (PDF)

357. Validation

CIOMS DILI 2020

A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose.

Source: 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)

358. Vulnerable populations

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Persons who are relatively or absolutely incapable of protecting their own interests.

This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests.

In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests.

Modified from: Guideline 15. In: CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. 2016. (PDF)

Earlier/other definition(s):

Vulnerable

Clinical research in RLS 2021

In this report the term "vulnerable" describes persons or groups who may have an increased likelihood of being wronged or of incurring additional harm in research. In contrast, the term "special populations" is used to describe populations with physiological characteristics that warrant their being considered separately in clinical research, such as children, pregnant women and the elderly (see Appendix 1). The two categories may overlap.

Proposed by the CIOMS Working Group on Clinical Research in RLS.

{The definition is found in section 4.1 of the CIOMS Working Group report, see footnote 16.}

359. Weibull distribution

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

A distribution of data that is relevant to parametric survival analyses.

Proposed by CIOMS Working Group VI.

360. Weight

CIOMS X: Meta-analysis 2016 | (Japanese translation available, see page xii)

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.

361. Yate's correction

CIOMS VI: Clinical trial safety information 2005 | (Chinese translation available, see page xii)

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 Vaccine safety surveillance 2017

Probability that a specified event will occur in a specified population, in contrast to the relative risk of the event.

Source: http://medical-dictionary.thefreedictionary.com/absolute+risk, **accessed 5 May 2021**

→ Absolute risk (TERMS AND DEFINITIONS — GENERAL)

2. Active vaccine safety surveillance

CIOMS Vaccine safety surveillance 2017

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 the CIOMS Working Group on Vaccine Safety.

→ Active surveillance (TERMS AND DEFINITIONS — GENERAL)

3. Adverse event following immunization (AEFI) [1]

CIOMS/WHO Vaccine PV terms 2012

Adopted by: **CIOMS Vaccine safety surveillance 2017**

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.

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

[1] [Footnote 1 in the CIOMS/WHO 2012 Working Group 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.

{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.}

→ See also Adverse event (TERMS AND DEFINITIONS — GENERAL)

4. Aggregate data

CIOMS Vaccine safety surveillance 2017

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.

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

5. Background rates

CIOMS Vaccine safety surveillance 2017

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.

Source: Guide to the WHO information sheets on observed rates of vaccine reactions. Geneva: World Health Organization;12 April 2012. (PDF)

6. Clinical vaccine failure

CIOMS/WHO Vaccine PV terms 2012

{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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

7. Coincidental event

CIOMS/WHO Vaccine PV terms 2012

{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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

8. Common technical document

CIOMS Vaccine safety surveillance 2017

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.

Combined and modified 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

9. Immunization and vaccination

CIOMS/WHO Vaccine PV terms 2012

Adopted by: **CIOMS Vaccine safety communication 2018**

"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.**

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

{Clarifications in the 2012 report:}

*"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.

** 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").

10. Immunization anxiety-related reaction

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

{See also: Immunization stress-related response (ISRR)}

A range of symptoms and signs that may arise around immunization that are related to the stress around the procedure and not to the vaccine itself or the immunization programme, a defect in the quality of the vaccine or an error of the immunization programme. These reactions may include vasovagal-mediated reactions, hyper-ventilation-mediated reactions and stress-related psychiatric reactions or disorder.

Modified from: WHO Vaccine safety basics e-learning course, Module 3: Adverse events following immunization. (Webpage accessed 29 January 2022)

{The above link was no longer valid as of 29 July 2022. Alternative link: WHO Vaccine Safety Basics learning manual (PDF)}

Earlier/other definition(s):

Immunization anxiety-related reaction

CIOMS/WHO Vaccine PV terms 2012

{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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

*{*Note from the CIOMS cumulative glossary team, June 2021: *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 Vaccine PV terms 2012

{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[1] vaccine handling, prescribing or administration and thus by its nature is preventable.

[1] "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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

12. Immunization stress-related response (ISRR)

CIOMS Glossary Advisory Board, April 2023

A range of symptoms and signs that arise around vaccination and which are due to fear of the procedure. The response is considered NOT related to the vaccine product, nor any defect in the quality of the vaccine or any error in the immunisation programme, but is caused by a stress response to the procedure.

Proposed by the CIOMS Glossary Advisory Board. Modified from: WHO. Immunization stress-related response: a manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. (PDF)

13. Immunological vaccine failure

CIOMS/WHO Vaccine PV terms 2012

{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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

14. Knowledge gap

CIOMS Vaccine safety surveillance 2017

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.

M

15. Medicine or vaccine use within label, synonym: On-label use

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

Use of a medicinal product in accordance with the terms of the marketing authorisation.

Proposed by CIOMS Working Group XI.

→ TERMS AND DEFINITIONS – GENERAL: Medicine or vaccine use within label
See also: Antonym – TERMS AND DEFINITIONS – GENERAL: Off-label use

P

16. Passive vaccine safety surveillance

CIOMS Vaccine safety surveillance 2017

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)

→ Passive surveillance (TERMS AND DEFINITIONS — GENERAL)

S

17. Serious adverse event following immunization (AEFI)

CIOMS Vaccine safety surveillance 2017

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.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF)

→ Serious adverse event (TERMS AND DEFINITIONS — GENERAL)

Earlier/other definition(s):

Serious adverse event

CIOMS/WHO Vaccine PV terms 2012

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 CIOMS/WHO Working Group report:] Clinical safety data management: definitions and standards for expedited reporting. E2A. ICH, 1994. (PDF)

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

Proposed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance

18. Signal

CIOMS/WHO Vaccine PV terms 2012

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.

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).

Adopted from: CIOMS Working Group VIII on Signal Detection.

→ Signal (TERMS AND DEFINITIONS — GENERAL)

19. Significant knowledge gap

CIOMS Vaccine safety surveillance 2017

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 the CIOMS Working Group on Vaccine Safety.

{See also Knowledge gap}

20. Surveillance

CIOMS Vaccine safety surveillance 2017

The continuing, systematic collection of data that are analysed and disseminated to enable decision- making and action to protect the health of populations.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF)

V

21. Vaccine approval, authorization or licensure

CIOMS/WHO Vaccine PV terms 2012

Adopted by: **CIOMS Vaccine safety communication 2018**

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)

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

22. Vaccination failure

CIOMS/WHO Vaccine PV terms 2012

{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**).

[Reference 22 in the source 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 source 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.

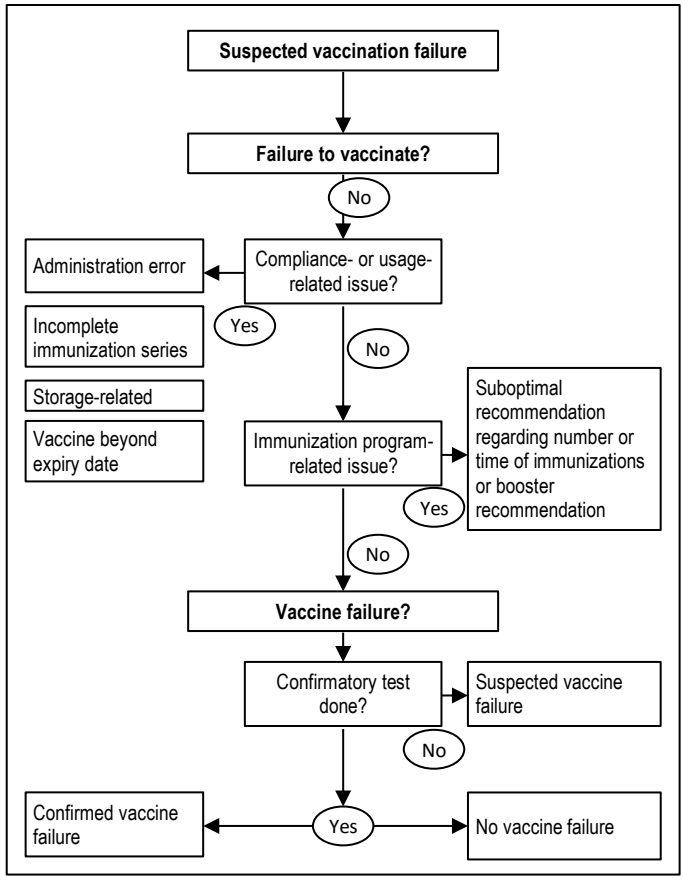
B. Failure to vaccinate: *(3) Usage issues:* (a) administration error; (b) vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s); (c) storage-related; (d) vaccine beyond expiry date when used. *(4) Immunization programme-related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

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

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

Figure 1: see next page

Figure 1: Vaccination failure algorithm



23. Vaccine failure

{See also Vaccination failure}

CIOMS/WHO Vaccine PV terms 2012

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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

24. Vaccine hesitancy

CIOMS XI: Patient involvement 2022 | (Japanese translation available, see page xii)

The delay in acceptance or the refusal of vaccination despite availability of vaccination services.

Modified from: MacDonald NE; SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015 Aug 14;33(34):4161-4. doi: 10.1016/j.vaccine.2015.04.036.

Earlier/other definition(s):

Vaccine hesitancy

CIOMS Vaccine safety communication 2018

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 CIOMS Working Group 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 the CIOMS Working Group on Vaccine Safety.

25. Vaccine pharmacovigilance

CIOMS Vaccine safety communication 2018

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.

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

Earlier/other definition(s):

Vaccine pharmacovigilance

CIOMS Vaccine safety surveillance 2017

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 Vaccine PV terms 2012

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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

26. Vaccine product-related reaction

CIOMS/WHO Vaccine PV terms 2012

{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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

27. Vaccine quality defect

CIOMS/WHO Vaccine PV terms 2012

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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

28. Vaccine quality defect-related reaction

CIOMS/WHO Vaccine PV terms 2012

{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[1] of the vaccine product including its administration device as provided by the manufacturer.

[1] 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 the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

29. Vaccine safety

CIOMS Vaccine safety surveillance 2017

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.

Source: WHO Global manual on surveillance of adverse events following immunization, 2014. (PDF)

30. Vaccine safety communication

CIOMS Vaccine safety communication 2018

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 the CIOMS Working Group on Vaccine Safety.

31. Vaccine safety communication plans (VacSCPs)

CIOMS Vaccine safety communication 2018

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 the CIOMS Working Group on Vaccine Safety.

32. Vaccine safety communication systems

CIOMS Vaccine safety communication 2018

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 the CIOMS Working Group on Vaccine Safety

END

The Council for International Organizations of Medical Sciences (CIOMS) looks back on several decades of strategic influence in pharmacovigilance. CIOMS convened its first pharmacovigilance working group in 1986 with the objective to harmonize the diverse requirements for adverse events reporting to medicines regulatory authorities. The standardized format proposed by the group, the CIOMS-I reporting form, was adopted globally. In the years that followed, new working groups targeted additional emerging aspects of pharmacovigilance, shaping the thinking and methodological approach. When the International Council for Harmonisation (ICH) was founded in 1990 to harmonize the regulatory requirements for pharmaceuticals, the CIOMS recommendations were taken up in several ICH Efficacy Guidelines, forming the basis of modern pharmacovigilance.

The science and practice of pharmacovigilance have evolved over the past decades, and so too have the related definitions. This glossary compiles all the definitions within the CIOMS Working Group reports on pharmacovigilance and related topics. The glossary does not cover CIOMS reports on the subjects of research ethics, pharmacogenetics, clinical pharmacology, publications on the development and use of standardised MedDRA® queries (SMQs), or publications resulting from CIOMS Roundtable Discussions (1967-1997). CIOMS is maintaining this glossary on its website and welcomes all feedback.

CIOMS cumulative glossary, with a focus on pharmacovigilance. Version 2.3. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2025.

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