

3. Adverse drug reaction (ADR)

The FDA's Guidance for Industry provides the following definition of adverse drug reactions (ADRs) (50):

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

4. Unexpected adverse drug reaction

The FDA's Guidance for Industry provides the following definition of unexpected drug reactions (51):

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

5. Potential confusion in defining adverse events

Defining terms used to characterize drug safety is not a trivial issue. Ioannidis et al. (52) find that some publications use the terms *side effects* and *adverse effects* to mean the same thing, thus creating confusion. Regarding this inappropriate use of terms, Ioannidis et al. (53) complain that some authors use the term *adverse events* synonymously with *side effects*. What is inappropriate is that the term *side effects* implies that the drug causes the side effect while, in contrast, the term *adverse effects* does not imply causality.

Moreover, the ICH Guidelines (54) expressly recommend not using the term *side effect*, writing that, "[t]he old term 'side effect' has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction."

⁵⁰ U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. E6 Good clinical practice: consolidated guidance (April 1996).

⁵¹ U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. E6 Good clinical practice: consolidated guidance (April 1996).

⁵² Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med.* 2004;141:781–788.

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⁵⁴ ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (June 1995).