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Confusions and ambiguities in the classification of adverse events in the clinical research

CONFUSÕES E AMBIGÜIDADES NA CLASSIFICAÇÃO DE EVENTOS ADVERSOS EM PESQUISA CLÍNICA

CONFUSIONES Y AMBIGÜEDADES EN LA CLASIFICACIÓN DE EVENTOS ADVERSOS EN INVESTIGACIÓN CLÍNICA

Gabriela Marodin[1], José Roberto Goldim[2]

ABSTRACT

It is quite common to consider the terms *ambiguous* and *confusing* as synonyms. Confusing information brings together various data with similar meanings. In ambiguous information, on the other hand, several meanings are assigned to a single word. Excessive information also generates ambiguity; therefore, a concise, clear language is demanded. The term *adverse event* (AE) is defined as any inconvenient medical occurrence suffered by a subject during a clinical investigation research. Confusion and ambiguity in the use of words may generate relevant consequences in the appraisal of AEs. The objective of this present theoretical study is to harmonize the vocabulary applied in the characterization of risks and in the communication of AEs in clinical research processes. AEs may be classified according to their predictability, frequency, gravity, causality, and severity. Regulatory documents usually address AEs in their severity and causality aspects. Vocabulary conformity in the communication of AEs is an essential step towards avoiding inaccurate use of words with confused or ambiguous meanings.

KEY WORDS

Biomedical research.
Ethics, research.
Bioethics.
Research subjects.

RESUMO

É comum considerar ambíguo como sinônimo de confuso. Em uma informação confusa, várias informações têm um mesmo significado. Na informação ambígua, ao contrário, vários significados são atribuídos a uma mesma palavra. Informações excessivas também geram ambiguidade, daí a necessidade de concisão e clareza na linguagem. O termo evento adverso (EA) é definido como qualquer ocorrência médica inconveniente, sofrida por um sujeito da pesquisa em investigação clínica. A confusão e a ambiguidade no uso de palavras podem gerar conseqüências importantes na valorização de EAs. O objetivo deste estudo, de natureza teórica, é harmonizar o vocabulário utilizado na caracterização dos riscos e na comunicação de EAs na pesquisa clínica. Os EAs podem ser classificados quanto à previsibilidade, frequência, gravidade, causalidade e seriedade. Muitas vezes, em documentos regulatórios, os EAs são definidos em função da seriedade e causalidade. A harmonização do vocabulário na comunicação de EAs é fundamental para evitar a utilização equivocada de palavras com sentido confuso, ou ambíguo.

DESCRITORES

Pesquisa biomédica.
Ética em pesquisa.
Bioética.
Sujeitos da pesquisa.

RESUMEN

Es común considerar ambiguo como siendo sinónimo de confuso. En una información confusa, varias informaciones tienen un mismo significado. En la información ambigua, al contrario, varios significados son atribuidos a una misma palabra. Informaciones excesivas también generan ambigüedad, por esa razón es necesario ser conciso y claro en el lenguaje. El término evento adverso (EA) es definido como cualquier ocurrencia médica inconveniente, sufrida por un sujeto participante del estudio, en investigación clínica. La confusión y la ambigüedad en el uso de las palabras pueden generar consecuencias importantes en la valorización de los EAs. El objetivo de este estudio, de naturaleza teórica, es armonizar el vocabulario utilizado en la caracterización de los riesgos y en la comunicación de los EAs en la investigación clínica. Los EAs pueden ser clasificados en cuanto a su previsibilidad, frecuencia, gravedad, causalidad y seriedad. Muchas veces, en documentos normativos, los EAs son definidos en función de la seriedad y causalidad. La armonización del vocabulario en la comunicación de EAs es fundamental para evitar la utilización equivocada de palabras con sentido confuso, o ambiguo.

DESCRIPTORES

Investigación biomédica.
Ética en investigación.
Bioética.
Sujetos de investigación.

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INTRODUCTION

Good Clinical Practice (GCP) guidelines are international scientific and ethical quality standards for the development, conduct, recording and reporting of health research involving human subjects. Compliance helps to ensure the protection of human rights of participants in a clinical trial[1]. A Research Ethics Committee (REC) evaluates and follows research projects[2]. The process of evaluating adverse events (AEs) helps to establish risk/benefit ratio. In project implementation and follow-up activities, monitoring AEs is crucial.

In 1993, the International Ethical Guidelines for Research Involving Human Beings were published by the Council for International Organizations of Medical Sciences (CIOMS)[3], associated to the World Health Organization (WHO). In 2002[4], they were reviewed. In 1996, in Brazil, the National Council of Health (NCH) Resolution 196/96 established, in item V.4, that the

> Research Ethics Committee of the institution should be informed of all AEs, or relevant facts that can alter the normal course of the study[2].

The NCH Resolution 251/97 on research regulations for new drugs, medications, vaccines and diagnosis tests, implies (item III.2.d) that the responsible researcher must *report to REC any events of AEs and /or unwelcome adverse reactions*[5].

One of the limitations regarding the evaluation and follow-up of AEs is the exact meaning of these terms. Inappropriate use generates ambiguity and confusion. The lack of concise language and understanding damage evaluations and reports of AEs in clinical research. The aim of this work is to harmonize the vocabulary used in describing these risks and reporting of AEs in clinical research.

CONFUSION AND AMBIGUITY

Ambiguity is the obscurity of the meaning in words and phrases. Also, it carries a sense of hesitation, doubt and indecision between two or more possibilities, and even multiple meanings[6]. Ambiguous is commonly considered a synonym for confusing. In confusing information, different information has the same meaning. In contrast, with ambiguous information, many different meanings are attributed to a single word. Excessive information also leads to ambiguity. Therefore, the need for concision and clarity of ideas in language work is imperative.

The term AEs is defined as any inconvenient medical occurrence, experienced by one of the research's subjects or individual under clinical investigation. Confusion and ambiguity in the use of words can lead to important consequences in the importance of AEs. AEs can be classified as for their predictability, frequency, intensity, attribution, and seriousness

AE intensity is classified as mild, moderate, serious, or lethal[7]. Different authors confuse this classification with a serious adverse event (SAE). They are classified according to the consequences resulting from such event. An SAE implies death, hospitalization, prolonged hospitalization, or any other relevant consequence to the medical point of view; including persistent or significant deficiency/incapacity, and congenital/defect[1]. The term *serious* is frequently used to describe the intensity of a specific event (as in a mild, moderate or serious myocardial infarction); however, the event itself can have a relatively smaller clinical meaning (as serious headache). It does not mean the same as *serious*, which is based on the consequence of the event; or in action criteria commonly associated to events that are life threatening or represent a threat to the patient's life. Therefore, a serious-intensity AE (serious nausea) can occur not demonstrating any relation applied to the SAE term, low-repercussion clinical event, namely non-serious. However, a moderate-intensity AE resulting in hospitalization is considered as SAE

ADVERSE EVENTS

AEs, defined as unintentional complications resulting from the care provided, are acknowledged as one of the most important problems in the health area[8]. An AE is any unwelcome medical occurrence during a treatment with a pharmaceutical product, however not necessarily presenting a causing relation to the treatment[9]. As for a change in the study focus that evolved from a medical legal feature into studies on quality improvement, the AE was then defined as an unintentional injury resulting in a temporary or permanent incapacity and/or prolonging the stay period or presenting death as a consequence of the care provided[10]. For example, any allergic episode is an AE. If a patient using a certain drug presents an allergy, it does not imply that it is resulting from the use of the drug. Another identifying factor, not related to the medication, can be the generating factor. However, the health professional should not include, beforehand, that an allergy is resulting from this factor[11]. After finding the AE, the cause-effect relation must be investigated between the allergy and the medication.

An AE can be any inconvenient medical event experienced by a research subject or individual under clinical investigation with pharmaceutical products that does not necessarily presents a causing relation with this treatment. It can be an unfavorable and unintentional sign, symptom or temporary disease associated to the use of a medical product under investigation; whether or not related to this product[1].

A SAE is any unwelcomed medical occurrence, under any prescribed dose that: results in death; represents a life risk; requires hospitalization of the research subject, or prologues a pre-occurring hospitalization; results in significant or persistent incapacitation/incapacity; causes congenital defect/anomaly[1].

The unexpected adverse reaction to a drug is a natural reaction or intensity non-consistent to the applicable information of the mentioned product (example: Investigator's Brochure for the product under investigation, not yet approved), or instruction/summary of pharmaceutical characteristics for approved products[1].

When a medication or drug is administrated in a study, apart from the useful therapeutic effects, in some people, some unwanted effects are also observed. There are no adverse reaction risk-free drugs. The probability of occurrence can vary, the reaction can be mild, or serious, perhaps predictable or not, however, the doctor/researcher and the research patient/subject should always be aware of this possibility.

Classification of adverse effects (AEs)

Regarding AEs, they can be classified as for their predictability, frequency, intensity, attribution, and seriousness (Table 1).

Table 1 - Classification of Adverse Effects - Porto Alegre - 2007

ADVERSE EVENTS				
Before			After	
Predictability	Frequency	Intensity	Causality	Seriousness
Predictable Already reported in other studies **Unpredictable** Unknown (Uncertainty)	**Very rare** < 0,01% **Rare** ≥ 0,01% and < 0,1% **Not common** ≥ 0,1% and < 1% **Common** ≥ 1% and < 10% **Very common** ≥ 10% **Not quantified** Chance	**Mild** Short Duration Neither requires medication nor treatment suspension. Not causing or lingering hospitalization **Moderate** Therapeutic modification No need for suspending medication May cause or linger hospitalization Requires specific treatment **Severe** Potentially lethal Hospitalization or the lingering of it. Medication suspension Specific treatment **Lethal** Life-threatening	**WHO** / **NARANJO** **Defined** / **Defined** **Probable** / **Probable** **Possible** / **Possible** **Improbable**, **Conditional**, **Unclassifiable**, **Classifiable** / **Unlikely or Unrelated**	**Not serious** **Serious** Lingering of hospitalization Hospitalization Death Other

Adverse effects as for predictability

Regarding predictability, the AEs are those already described in literature, in the product's description, in the investigator's manual, or in the study protocol. Unpredicted AE is the one not yet described, including events that may be symptomatically and physic-pathologically related to another one already described, but different from this event due to their gravity and specificity degree.

Adverse events as for frequency

Regarding frequency, AE are considered as: very common, when frequency is higher or equal to 10.00%; common, higher or equal to 1.00% and lower than 10.00%; uncommon, higher or equal to 0.10% and lower than 1.00%; rare, higher or equal to 0.01% and lower than 0.10%; very rare, lower than 0.01%[12].

Adverse events as for intensity

AEs as for their intensity are classified as mild, moderate, serious, or lethal[7], according to their intensity and the verified events.

The intensity of adverse alterations in physical signs or symptoms will be regarded as: mild, of short term, not requiring specific treatment neither medication suspension, there is neither the need for antidotes nor for hospitalization; moderate, altering patient's normal activities, requiring medication therapy changes, despite not being necessary to suspend the causing drug, they can cause or pro-

long hospitalization and require specific treatment; serious, are potentially lethal, requiring interruption of the drugs and the specific treatment, they require hospitalization or prolonging patient's stay in the hospital; lethal, they directly or indirectly cause the death of the patient[7].

The WHO also considers four categories of intensity: 1) mild: little importance reactions and short active period, they may require treatment, but they do not substantially affect patients' normal life course; 2) moderate: alter patients' normal activities, resulting in transitory incapacity with no sequels, causing hospitalization, prolonging hospital stay, urgency care and service, absence at work or school; 3) serious: reactions directly threatening patients' life, congenital anomalies, resulting in permanent or significant incapacity, or needing intervention to avoid sequels; 4) lethal: reactions that lead to the death of the patient[13].

Adverse events as for attribution

Regarding attribution, an AE can be associated to the performed intervention – cause/effect retrospective relation – classified as follows: definite, probable, possible, or unlikely or unrelated[7]. However, the WHO considers the following attribution categories: definite, probable, possible, improbable, conditional (unclassified) and unclassifiable (not accessible), depending on the security level of the cause-effect relation[14].

Definite: clinical event, including abnormalities in laboratorial tests, occurring within plausible time in relation to the administration of the medication and that cannot be explained by the base disease or by other medication or even chemical substances. The response to suspending the use of this medication must be clinically plausible. The event must be pharmacologic, or resulting from a definite phenomenon, using a satisfying re-introduction procedure, if needed[14].

Probable: clinical event, including abnormalities in laboratory tests occurring under a reasonable administration period for the medication that cannot probably be attributed to a concomitant disease or other medication, chemical substances and that present a reasonable clinical response to the suspension of this medication. Re-introduction information is not needed to complete this definition[14].

Possible: clinical event, including abnormalities in laboratory tests occurring under a reasonable administration period for the medication, however they can also be explained by a concomitant disease or other medication or chemical substances. Information on the interruption of the medication can be absent or obscure[14].

Improbable: clinical event including abnormalities in laboratory tests that present a transitory relation to the administration of a medication; causing an improbable causing relation and that in other medication, chemical substances or subjacent diseases, propitiate plausible explanations[14].

Conditional/unclassified: clinical event, including abnormalities in laboratory tests, notified as an AE, where more data is needed for an appropriate evaluation, or when additional data are being analyzed[14].

Unclassifiable/non-accessible: Notification suggesting an AE that cannot be evaluated, since information is not sufficient or contradictory and that cannot be completed or verified(14).

The WHO segments unlikely or unrelated attribution into improbable, conditional, or unclassifiable. Thus, attribution can be characterized by six categories: definite, probable, possible, improbable, conditional and unclassifiable[14].

Adverse events as for seriousness

Seriousness classification comprises serious and non-serious AEs. They are classified due to the consequences resulting from such event. A serious AE results in death, hospitalization, prolonging hospital stay or other relevant consequences under the medical point of view[1]. According to the Collegiate Board Resolution RDC 339 of June 5, 2008, in item X, SAEs are defined as those resulting on any adverse experience with drugs, or biologic products or devices, occurring within any dose and that result in any one of the following: death, potentially lethal AE (an effect that sets the patient under immediate death risk due to the occurred AE); persistent or significant incapacity/disability; requiring hospitalization or prolonging pre-existing hospital stay; congenital anomaly or birth defect[15]. A non-serious AE is any AE that does not fulfills the criteria of a SAE.

RESEARCH ON NEW DRUGS: ASSOCIATED RISKS

The clinical phase of the research with new medication contains four phases, I to IV, depending on the knowledge level presented on these drugs' effects in cellular, animal and human models. Specific objectives from each type of study are used; the type of outline, the number of participants, and their characteristics. Phases are successive and scaled with increasing complexity and exposition levels[16].

The NCH Resolution 251/97[5] incorporates the decisions in the NCH Resolution 196/96[2] on Guidelines and Regulating Norms for the Research Involving Human Beings, which is a complementary part of the research area with new drugs, medication, vaccines and diagnosis tests.

Phase I studies are carried out on small groups of volunteers, generally healthy, of a new active principle or formulation. Depending on the specialty and objective of the research, Phase I studies can be carried out directly on specific groups as carriers of irreversible chronicle diseases as oncology, psychiatric disorders or altered kidney function patients[5-17].

Studies on Phase II are pilot therapeutic studies to demonstrate the activity of establishing short term safety of

the active principle in patients affected by a specific disease or pathologic condition. They are carried out on a limited number of participants and frequently followed by an administrative study with a view to establish the dose-response relation[5]. Phase IIa and IIb comprise dose titling and efficiency.

Initial Phase II studies (phase IIa) use drug doses already tested as safe on Phase I studies. They regard studies aimed at evaluating the tolerability and safety of these new drugs[18]. Samples are small and follow rigid control measures[17].

Phase II advanced studies (phase IIb) are conducted on larger samples with well defined inclusion criteria. They have the objective of adding data related to the drug's efficiency[18]. Even with a short period of follow up, the occurrence of some AEs can be verified.

Phase III studies are amplified therapeutic studies carried out in large, varied groups of patients. They aim at determining the short and long term risk/benefit results of active principle formulations, and, generally their therapeutic value. With a view to establish and approve the presumed benefit. In this phase, the most frequent adverse reactions type of profile is explored as well as the medication special characteristics[5].

Phase III studies were recently subdivided into phases IIIa and IIIb. The purpose of the first phase is to evaluate the efficiency of drugs already tested in Phase I and II studies. Phase IIIb studies are carried out while the application for registration of a new drug is being issued. The phase increases the observation period for medication effects[18].

Continuous clinical monitoring of phase III studies is needed for providing an appropriate follow up of the process of recruiting and selecting participants, and also the credibility and quality of data, research subjects follow up and AEs evaluation. This is especially relevant for SAEs since they involve prolonging hospital stay, the need for hospitalization, or the death of the participant.

If the product is within acceptable toxicity standards, it is approved. However, since the number of patients in phase III rarely reach more than ten thousand, it is still difficult to establish adverse incidence lower than 1:20.000[11].

Phase IV studies are researches with a view to monitoring, or post-selling vigilance of the drug. They aim at establishing the therapeutic value, on large scale, and the appearance of new adverse reactions, as the less frequent reactions and/or the confirmation for those already known and treatment strategies[5].

According to item I.4 of NCH Resolution 251/97[5],

> in any clinical testing, and specifically in conflicts of interests involving new products' research, the dignity and well-being of the subject included in the research must prevail over other interests, whether economic, scientific or pertaining to the community.

According to national and international resolutions, every research project on new drugs, involving human beings, must be subjected to REC and must be followed by the Free and Informed Consent Form (FICF) and the researcher's manual. The manual, also known as the investigator's brochure, comprises information on pharmacokinetic and pharmacy dynamics data of the drug under study, toxicity studies, previously performed clinical studies (for instance, the same drug in other countries), predicted AEs; in other words, it comprises pre-clinical tests and clinical tests already carried out with this drug.

The project, researcher manual and the FICF must show, appropriately described, the AEs reported in clinical studies with the drug under investigation, allowing for knowledge and decision making by the subject regarding the participation in the research.

Researches on new drugs require attention both for the predicted risks evaluation and for monitoring AEs during project execution.

Two important and complementary stages are; risk evaluation and monitoring of AEs. The evaluation consists of verifying the predicted risks in the beginning of the research, whether in the Free and Informed Consent Form (FICF), in the project or in the investigator's manual. Monitoring happens through AEs reporting. They will be attached to the research, contributing for the dynamic decision making process. In case risks are higher than benefits, REC can re-evaluate the project, with a view to the participants' safety.

As the project is executed, the current AEs appear. Risk evaluation precedes this moment and allows for verifying if that AE was reported, and therefore, is predictable or, in case it was not reported, it stands uncertain. Already reported AEs can be classified according to frequency as very common, common, not common, rare and very rare[12]. Also, the intensity association, according to the intensity of the event, can be mild, moderate, serious or lethal[7]. However, monitoring occurs as the execution of the project, allowing for the classification of the event as for its attribution, based on the cause/effect retrospective relation, establishing the causing association between the drug and the occurring AEs under the following proposed categories by the WHO: definite, probable, possible, improbable, conditional and unclassifiable[14]. Based on the consequence/result, this event can be classified according to its severity as; non-serious, serious causing prolonging hospitalization, hospitalization, death, other significant event form the medical point of view[1] (Figure 1).

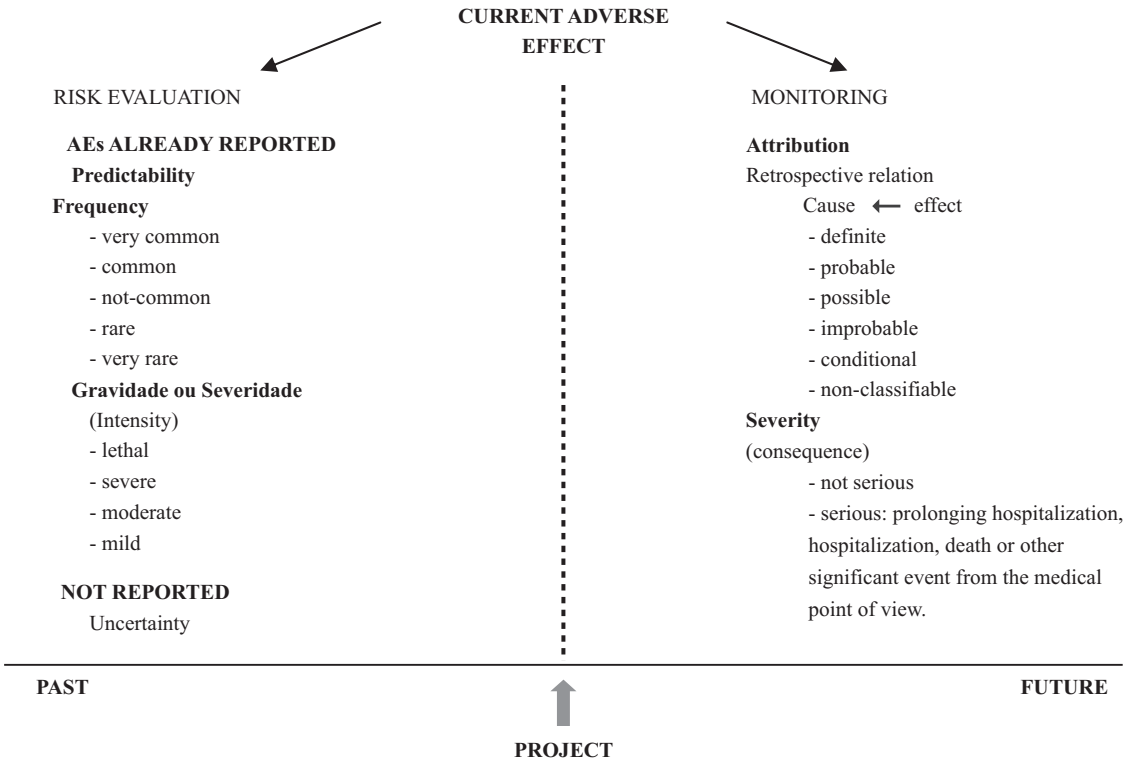

Figure 1 - Relation between time and adverse event - Porto Alegre - 2007

It is worth mentioning that risk evaluation is considered as those AEs predicted and quantified. In other words, that presents occurrences probability. AEs described and not-quantified are uncertain, where they can only present associated chances not considered as risks but as associated damages. Yet unpredicted AEs are unknown as for the beginning of the project.

In scientific research projects, we cannot dismiss the inherent risks: real, predicted and the unpredicted. Predicted risks are the known expected risks, already observed in similar projects, including in clinical testing using the same drug; they must be in the investigator's manual, in the project and in the FICF stating their probabilities and occurrence risks. Real risk is the AEs that occur. Unpredicted risk is an unexpected damage that occurs afterwards; something that was not expected and happened in reality. In the case where the real risk exceeds the predicted risk, the project must be reviewed.

CONCLUSION

Classification of AEs for predictability, frequency, and intensity are based on previous studies (preliminary studies and clinical phases I, II and III) with the experimental drug. However, AE classification regarding attribution and seriousness occurs afterwards, since they can only be classified throughout the execution of the project.

In most cases, even in regulatory documents, AEs are defined due to their seriousness and attribution. The importance of harmonizing the vocabulary in reporting AEs is crucial to avoid the erroneous use of confusing and ambiguous words.

Ambiguous information must be avoided, regarding more than one meaning that leads to lack of understanding, confusion, imprecision and lack of clarity. AE risk evaluation, as well as reporting and monitoring AEs, requires appropriate language so that authors and researchers themselves can understand them; if not, evaluation and monitoring activities can be damaged.

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