National Health Surveillance Agency

MANUAL FOR NOTIFICATION OF EVENT ADVERSE AND SAFETY MONITORING IN CLINICAL TRIALS

General Medicines Management - GGMED

Coordination of Clinical Research in Medicines

e Biological Products – COPEC

2016

MANUAL FOR NOTIFICATION OF ADVERSE EVENTS AND SAFETY MONITORING IN CLINICAL TRIALS

This Manual aims to guide professionals in the area with information on how to apply Resolution RDC/Anvisa nº 9 of February 20, 2015, contributing to the development of safe actions, in addition to providing relevant and updated information that can be better clarified through Manual instrument.

The Manual does not create new obligations, and must be used by public and private agents as a reference for compliance with existing legislation.

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SUMMARY

1. CONFIDENTIAL

EA - Adverse Event
EAG – Serious Adverse Event
EC - Clinical Trial
WHO - World Health Organization
RDC - Resolution of the Collegiate Board of Directors
SUSAR - *Suspected Unexpected Serious Adverse Reaction*
WHO - *World Health Organization*
WHOART - *The WHO Adverse Reactions Terminology*
WHO-UMC – The *WHO Uppsala Monitoring Centre*

2. INTRODUCTION

The publication of the regulation on Clinical Trials with drugs in Brazil brings the notification of adverse events as one of the forms of safety monitoring that the sponsor must carry out during the development of the investigational drug. This manual is intended to provide guidance for the Sponsor, Independent Safety Monitoring Committee, Investigator or Legal Representatives, when appropriate, to properly monitor safety and report adverse events in clinical trials.

This is a non-binding regulatory measure adopted as a complement to health legislation, with the educational purpose of providing guidance on routines and procedures for compliance with legislation, not intended to expand or restrict established technical or administrative requirements.

3. BASE LEGAL

Anvisa Resolution - RDC No. 9, of February 20, 2015, which provides for the regulation for conducting clinical trials with drugs in Brazil.

4. OBJECTIVE

Without prejudice to existing provisions in legal provisions, this manual aims to guide safety monitoring and adverse event notifications, as described in chapter VI of RDC No. 09/2015. We recommend that the format be standardized in terms of order and content to facilitate evaluation.

5. ADVERSE EVENT MONITORING (EA)

It is the sponsor's responsibility to collect and monitor all adverse events, including non-serious ones, classifying them according to Table 2 of the WHO UMC System for Standardized Causality Assessment (Annex I). Late adverse events should have an established monitoring plan.

All adverse events should be treated and affected participants followed up by the principal investigator and his/her team until their resolution or stabilization.

In case of a serious adverse event, the sponsor and the investigator must take immediate safety measures to protect the clinical trial participants against any imminent risk and the sponsor must notify Anvisa and describe the measures adopted from item 79 of the Notification Form of Serious Adverse Events in Clinical Trials available at Anvisa's Electronic Portal > Medicines > Clinical Research > Adverse Events > Form for Notification of Serious Adverse Events in Clinical Trials – Notivisa EC.

Analysis of aggregated data of adverse events occurring in clinical trials is part of monitoring.

6. NOTIFICATION OF EAGs (FORMSUS)

For regulatory submission purposes, the sponsor is required to report serious, unexpected adverse events occurring in the national territory, whose relationship with the investigational product is possible, probable or defined.

a) The recommended criterion for the individual categorization of each event into possible, probable, definite, unlikely, conditional or inaccessible is the system WHO-UMC for standardized causality assessment;
b) Other methods may be used for categorization as long as it is proven correspondence with the WHO-UMC system;
c) The Suspected Unexpected Serious Adverse Reaction (SUSAR) is included in the criteria for reporting a serious adverse event and must be notified, however, the criteria listed in the RDC are not limited to it.
d) Notifications must be made exclusively through the electronic form “Notification of EAGs in Clinical Trials with Medicines or Biological Products – Notivisa EC”, available on Anvisa's Electronic Portal > Medicines > Clinical Research > Adverse Events > Event Notification Form Serious Adverse Effects in Clinical Trials – Notivisa EC.

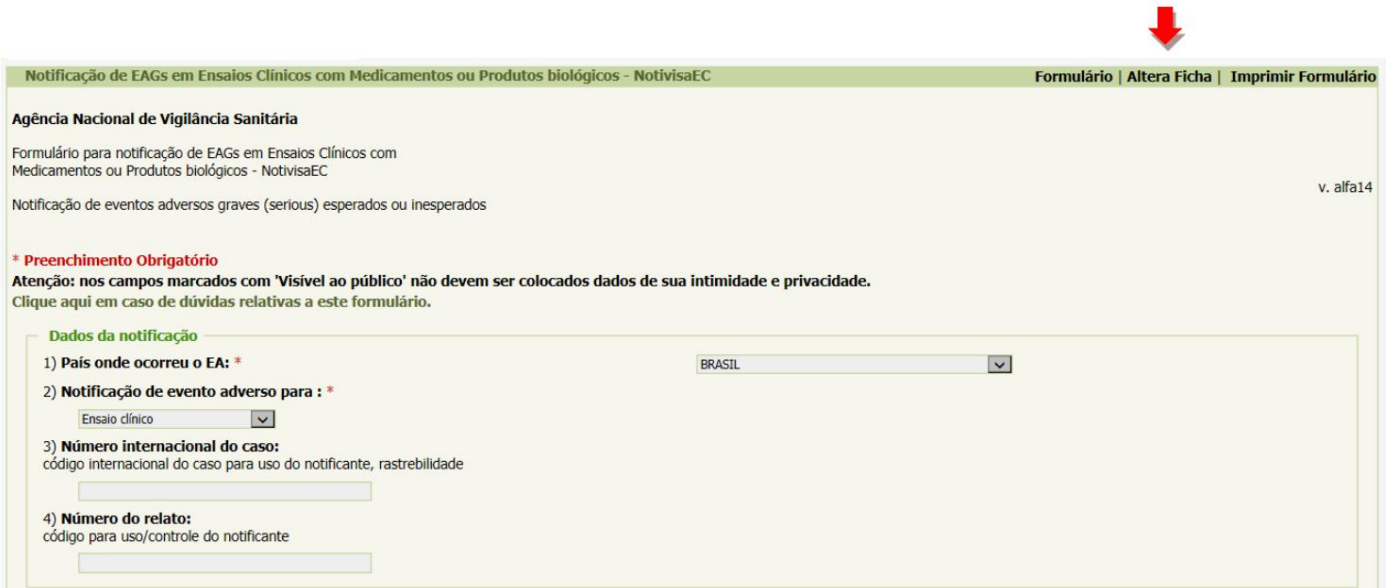
- Some form pages may take a while to load, please hold up;
- It is not necessary to log in to report adverse events;
- After filling in the last page, a protocol number will be generated and a notification mirror. Keep this number to update your notification;

- If the system becomes temporarily unavailable, the notification must be be sent as soon as the system returns;
- If there is any difficulty or doubt, whether in relation to the correct way of filling in the notification data or an information technology issue, contact Anvisa through the official communication channel. Specify that the inquiry refers to “reporting of adverse events in clinical trials” or enter this information in the request data.

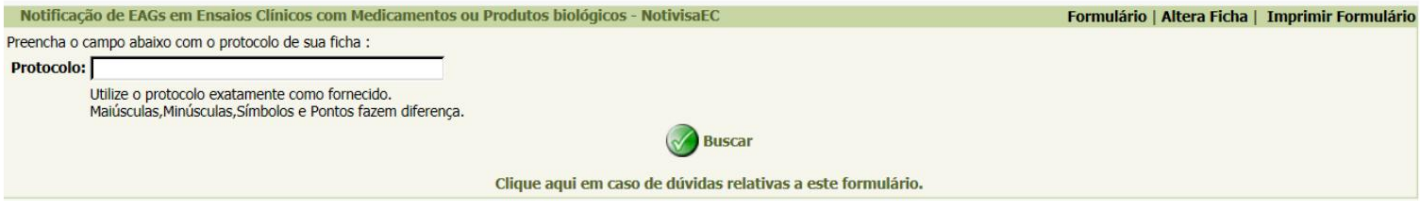
6.1 TRACEABILITY

All updates regarding evolution and other data must be made in the initial notification by changing the follow-up field.

- To access the AE notification, access: Anvisa Electronic Portal > Medicines > Clinical Research > Adverse Events > Form for Notification of Serious Adverse Events in Clinical Trials – Notivisa EC > Altera Ficha.



• Enter the notification protocol to retrieve it and update the information.



7. SUBMISSION OF OTHER EAs (SECURITY UPDATE REPORT)

The aggregated data of all other adverse events that are not categorized as serious and unexpected, whose relationship to the investigational product is not possible, probable or defined should be systematically evaluated by the sponsor or the Independent Safety Monitoring Committee and the results of this evaluation should be submitted to Anvisa in the Experimental Drug Development Safety Update Report.

The safety update report aims to understand, review and annually evaluate safety information collected during the investigation period of the investigational drug, marketed or not.

a) For regulatory submission purposes, these reports must be secondary electronic petitions linked to the DDCM case number.

b) The linking of secondary petitions to the corresponding processes is fundamental for their analysis and traceability in the systems electronics from Anvisa.

c) The subject of petition 10825 - CLINICAL TRIALS - must be used Drug Development Safety Update Report Experimental;

d) All DDCM modifications not considered substantial must be submitted to ANVISA as part of the investigational drug development safety update report;

e) It is recommended that the Security Update Reports of the Experimental Drug Development are presented in the *ICH Development Safety Update Report* (DSUR), *Guideline E2F Step* 5 format;

f) The sponsor must annually send Anvisa Update Reports of Safety of Experimental Drug Development, filed within a maximum period of 60 (sixty) consecutive days with reference to

annuality the date of approval of the DDCM by ANVISA or the date determined in the international development.

8. WHEN NOT TO NOTIFY THE ADVERSE EVENT TO ANVISA

The adverse event does not need to be reported to Anvisa when it occurs outside the national territory and when the adverse event was defined in the clinical trial protocol as a primary or secondary outcome.

9. TERMINOLOGY

Adverse event reporting should be made using the terminology from *"The WHO Adverse Reactions Terminology" (WHOART)* to specify the adverse event.

The term *serious* must be translated as "grave" in Portuguese and Spanish, according to the *"WHO Collaborating Center for International Drug Monitoring. Safety Monitoring of Medicinal Products: Guidelines for setting up and running a Pharmacovigilance Centre."*

10. QUALIFIER INTENSITY FOR HEALTH CONDITIONS (WHO)

Light

A problem is present less than 25% of the time, with an intensity that a person can tolerate and that rarely happens in the last 30 days.

moderate

It means a problem that is present less than 50% of the time, with an intensity, that is interfering with people's daily lives and that happens occasionally in the last 30 days.

Severe

It means a problem that is present more than 50% of the time, with an intensity that partially alters people's daily lives and that occurs frequently in the last 30 days.

full commitment

It means a problem that is present more than 95% of the time, with an intensity that completely changes the person's day-to-day and that has occurred every day for the last 30 days.

Not specified

It means that there is not enough information to specify the intensity.

Not applicable

It means that it is inappropriate to use a gradation (eg menstrual functions).

11. INDEPENDENT DATA AND DATA MONITORING COMMITTEE SAFETY

In the case of development of a phase III clinical trial, the monitoring must be accompanied by Independent Safety Monitoring Committees and their recommendations must be reported to Anvisa by the sponsor. In cases where there is no constitution of a safety monitoring committee, its absence must be justified, according to RDC 09/2015

The constitution of the committee, rules and functioning, members, conflict of interest, meetings, communications and recommendations must follow the Operational Guidelines for the Establishment and Functioning of Data Monitoring and Security Committees / Ministry of Health, World Health Organization. – Brasília: Ministry of Health, 2008. 44 p. – (Series A. Standards and Technical Manuals).

12. GLOSSARY

I - Clinical trial - research conducted in humans with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the investigational drug and/or identifying any adverse reaction to the investigational drug and/or studying the absorption , distribution, metabolism and excretion of the investigational drug to verify its safety and/or efficacy;

II - Adverse Event - any adverse medical occurrence in a patient or clinical trial participant to whom a pharmaceutical product was administered and which does not necessarily have a causal relationship to the treatment. As a result, an AE can be any unfavorable and unintended sign, symptom, or illness (including results outside the reference range) associated with the use of an investigational product, whether related to it or not;

III - Serious Adverse Event - one that results in any adverse experience with drugs, biological products or devices, occurring at any dose and resulting in any of the following outcomes:

a) death;

b) threat to life;

c) persistent or significant disability/disability;

d) requires hospitalization or prolongs hospitalization;

e) congenital anomaly or birth defect;

f) any suspicion of transmission of an infectious agent through a drug or;

g) clinically significant event.

IV - Unexpected Adverse Event - event not described as an adverse reaction in the investigational drug brochure or package insert.

V - Experimental drug - pharmaceutical product under test, object of the DDCM, to be used in the clinical trial, in order to obtain information for its registration or post-registration;

VI - Product under investigation - experimental drug, placebo, active comparator or any other product to be used in the clinical trial;

VII - Clinical Trial Protocol - document that describes the objectives, design, methodology, statistical considerations and organization of the trial. It also provides the context and rationale for the clinical trial;

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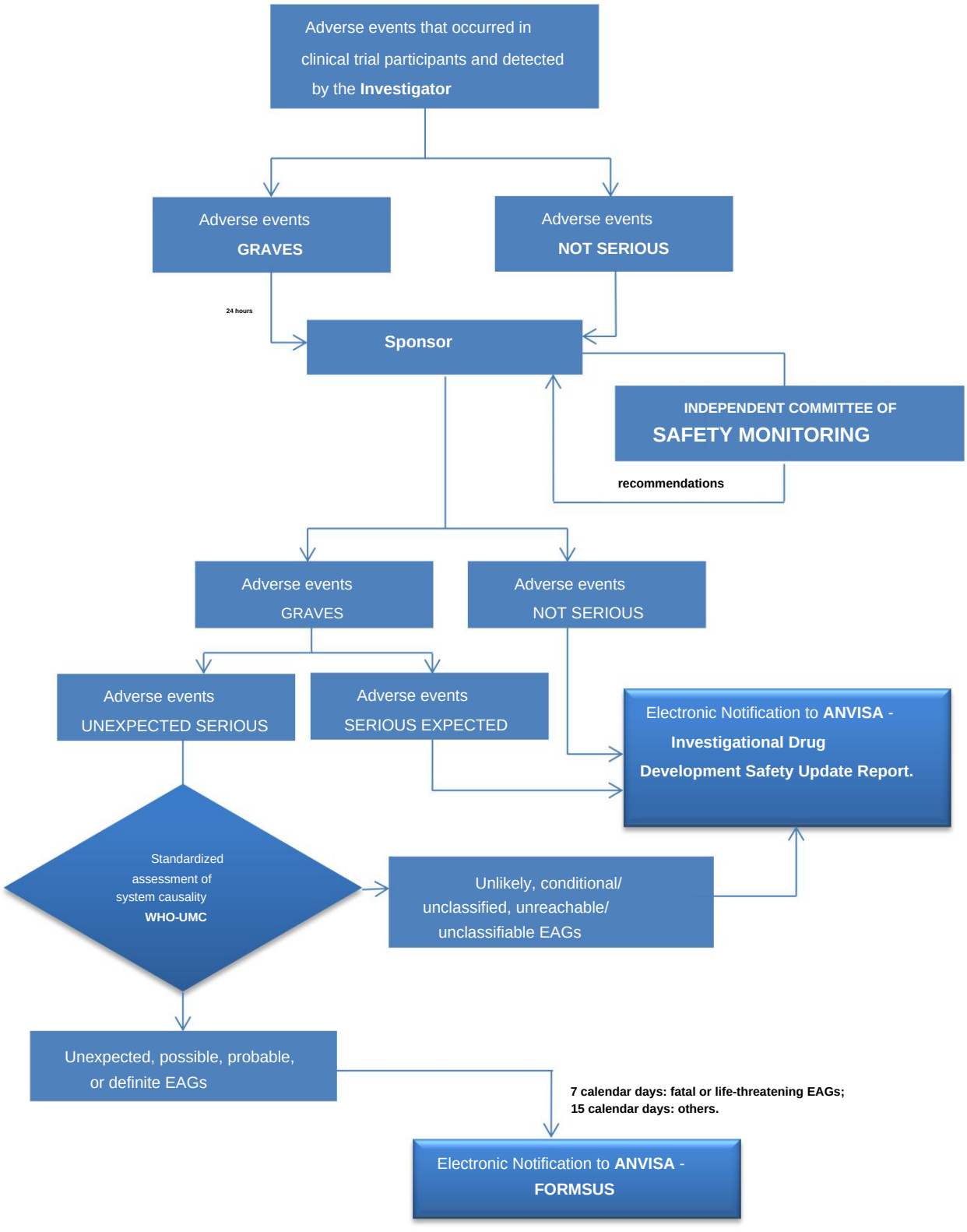
14. PROCESS FLOW CHART

14.1 ADVERSE EVENT NOTIFICATION FLOWCHART IN CLINICAL TRIALS



15. ANNEXES

15. 1 WHO-UMC SYSTEM FOR STANDARDIZED ASSESSMENT OF CAUSALITY

15.1.1 Table 1. System advances and limitations for standardized causality assessment

What can causality assessment do?	***What does causality assessment can not do?***
Decrease the disagreement between evaluators	Provide an accurate quantitative measure of the probability relationship
Classify probability ratio	Distinguish valid from invalid cases
Mark reports individually	Prove the relationship between the drug and the event
Improve scientific, educational assessment	Quantify the drug's contribution to the development of an adverse event
	Changing uncertainties to certainties

15.1.2 Table 2. WHO-UMC Categories of Causality

Categories+	*Criteria in the assessment of causality++*
Certain/Definite	• Event or (abnormal) change in laboratory examination with a plausible temporal relationship to the administration of the intervention; • Cannot be explained by illness or other intervention, medication; • Response to plausible interruption or withdrawal (pharmacologically, pathologically); · Pharmacologically or phenomenologically defined event (ie an objective and specific disorder or pharmacologically recognized phenomenon); • Satisfactory re-exposure, if necessary.
Likely	• An (abnormal) event or change in a laboratory test with a reasonable temporal relationship to the administration of the intervention; • Unlikely to be attributed to a disease or other intervention, medication; • Clinically reasonable response to discontinuation or withdrawal; • Reexposure not required.
Possible	• An (abnormal) event or change in a laboratory test with a reasonable temporal relationship to the administration of the intervention; • It can also be explained by illness or other interventions, medications; • Information about withdrawal or discontinuation of treatment may be missing or unclear.
Unlikely	• Event or change (abnormal) in laboratory examination that in relation to the time of administration of the intervention makes an unlikely (but not impossible) relationship; • Illness or other treatments provide plausible explanations.
parole / not classified	• Event or change (abnormal) in laboratory examination; • More data is needed for a proper assessment, or; • Additional data under investigation.

Inaccessible/ unclassifiable	• The narrative of the report suggests an adverse reaction; • Cannot be classified because the information is insufficient or contradictory; • Data cannot be supplemented or verified.

[+] Terms for the relationship

[++] To classify the relationship using one of the terms, the aspects observed must be reasonably within the criteria presented.

16. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st edition	Initial release	