ANVISA
Agência Nacional de Vigilância Sanitária

MANUAL FOR REPORTING SUSPECTED SERIOUS AND UNEXPECTED ADVERSE REACTIONS (SUSARs) AND SECURITY MONITORING IN CLINICAL TRIALS

COORDINATION OF CLINICAL RESEARCH IN MEDICINES AND BIOLOGICAL PRODUCTS (COPEC)
SECOND DIRECTORATE (DIRE2)

National Health Surveillance Agency – Anvisa

2025

SUS
ANVISA Agência Nacional de Vigilância Sanitária
MINISTÉRIO DA SAÚDE
GOVERNO FEDERAL BRASIL UNIÃO E RECONSTRUÇÃO

MANUAL FOR REPORTING SUSPECTED SERIOUS ADVERSE REACTIONS AND (SUSARs) AND SAFETY MONITORING IN CLINICAL TRIALS

This manual aims to guide the sponsor of clinical trials with drugs and biological products or a delegated Clinical Research Representative Organization (CRO) on how to perform safety monitoring and report Suspected Unexpected Serious Adverse Reaction (SUSARs) to Anvisa, without prejudice to the provisions of the current legal provisions.

It also aims to guide the investigator on how to carry out safety monitoring in order to minimize risks to clinical trial participants.

This manual 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 the legislation, and is not intended to expand or restrict established technical or administrative requirements.

Second Directorate – DIRE2

Organization - Anvisa

Coordination of Clinical Research in Medicines and Biological Products

Technical Preparation and Review

Adriane Alves de Oliveira

Claudio Martins Alves de Sousa

Christiane Santiago Maia

Flavia Regina Souza Sobral

Juliana Carvalho Rocha Dornelles

Kellen of Rocio Malaman

Kellen Christina de Freitas Gissoni

Maryangela Rezende Mascarenhas Santos Mota

Miriam Motizuki Onishi

COPEC Team – Anvisa

Adriane Alves de Oliveira

Andre Luis

Andrew Louis Carvalho Santos Souza

Bruno Coutinho

Carlos Augusto Martins Netto

Carolina Pingret Cintra

Claudio Martins Alves de Sousa

Edmilson Baptist of the Saints

Fanny Birth Moura Viana

Fernando Casseb Flosi

Flavia Regina Souza Sobral

Juliana Carvalho Rocha Dornelles

Kellen of Rocio Malaman

Leonardo Fabio Costa Jr.

Maira Reis Côgo

Maryangela Rezende Mascarenhas Santos Mota

Matheus Gabriel de Oliveira

Meiruze Sousa Freitas

Miriam Motizuki Onishi

Simone Vitoriana de Lima Nogueira

Sonia Costa e Silva

Summary

1. ACRONYM

Anvisa – National Health Surveillance Agency
AREE - Equivalent Foreign Regulatory Authority
CMDS - Independent Data and Safety Monitoring Committee
CTCAE - Common Terminology Criteria for Adverse Events
EA - Adverse Event
EAG - Serious Adverse Event
EC - Clinical Trial
ICH - International Council for Harmonisation of Technical Requirements for *Pharmaceuticals for Human Use*
Registration of Medicinal Products for Human Use)
WHO - World Health Organization
ORPC - Clinical Research Representative Organization
RDC - Resolution of the Board of Directors
SUSAR - Suspected Unexpected Serious Adverse Reaction

WHO - World Health Organization
WHOART - WHO Adverse Reactions Terminology
WHO-UMC - WHO Uppsala Monitoring Centre
Uppsala)

2. INTRODUCTION

The development of new medicines and biological products is structured around the conduct of well-designed non-clinical and clinical trials.

The risks to the safety of participants in a clinical trial have two main sources: the experimental drug and other intervention(s). Thus, from the
By conducting clinical trials, it is possible to collect important information on safety and efficacy, in addition to assessing the quality of the experimental drug. In this logic, the promotion and monitoring of safety become one of the pillars for conducting safe clinical trials, and it is essential to monitor the clinical development of drugs, aiming, among other aspects, to collect and update safety information.

Collecting adverse events, whether serious or not, is one of the main means of assessing the benefit-risk ratio of an experimental drug. By integrating these data with other sources, such as nonclinical findings, information from drugs in the same class, and preliminary efficacy data, it becomes possible to begin outlining the drug's safety profile.

The conduct of clinical trials in Brazil follows rigorous standards that prioritize quality
and efficacy of the drug under development and, mainly, the safety of the participants. To this end, RDC No. 945/2024, which regulates the conduct of clinical trials with drugs for registration purposes in Brazil, brings the notification of suspected serious and unexpected adverse reactions (SUSARs) as one of the ways of monitoring the safety of the clinical trial participants and as one of the responsibilities of the sponsor during the clinical development of the experimental drug.

Anvisa is a member of the International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use of
(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – ICH) and, therefore, adopts the model set out in the ICH E2B(R3) guide, operated nationally by VigiMed, for the electronic transmission of notification of SUSARs occurring in ongoing clinical trials in Brazil.

It should be noted that this notification reinforces the commitment to the protection of research participants and the continuous assessment of the benefit-risk balance of experimental drugs. Alignment with international guidelines, such as those of the ICH, strengthens the transparency and robustness of monitoring, contributing to the advancement of clinical research and the development of safe and effective drugs for the population.

3. LEGAL AND REGULATORY BASIS

The legal and regulatory framework that underpins the considerations presented here are:

Law 14,874, of May 28, 2024, which provides for research with human beings and establishes the National System of Ethics in Research with Human Beings.

Collegiate Board Resolution – RDC No. 945, of November 29, 2024, which provides guidelines and procedures for conducting clinical trials in the country with a view to subsequently granting drug registration.

4. OBJECTIVE

This manual is intended to guide security monitoring and notifications of Suspected Unexpected Serious *Adverse Reactions* (SUSAR) to Anvisa, as described in chapter VII of RDC No. 945/2024 and its updates, and in the guides cited in Bibliographic References, without prejudice to the determinations existing in the legal and regulatory provisions.

5. SECURITY MONITORING

According to ICH E8 (R1) guide, safety monitoring aims to protect clinical trial participants and characterize the drug's safety profile. Risks to participants should always be minimized, ensuring that the potential benefits of the clinical trial are more relevant, aiming to protect their rights, safety, dignity and well-being.

This monitoring is necessary to have a global view of the safety data of an intervention, as well as its results, to identify, evaluate and manage potential and real safety problems of the experimental drug. Thus, a
The close approach allows the adoption of quick and efficient measures to minimize risks to clinical trial participants, such as the temporary interruption of a study to assess possible changes in the benefit-risk balance of the drug.

To ensure adequate monitoring, it is important that procedures and systems for identifying, tracking and reporting safety issues are in place throughout the study.
are clearly defined. The approach to safety monitoring should reflect the type and objectives of the study, the risks to participants, and the level of knowledge available about the drug and the population being evaluated.

In order to have this global vision of safety, the sponsor or the ORPC, in a delegated manner, have the responsibility to collect, monitor and evaluate all adverse events, including non-serious ones, as well as all events that may impact the safety of clinical study participants.

The investigator is responsible for adopting immediate safety measures to protect the clinical trial participant against any imminent risk, and also for communicating the occurrence of any adverse events to the sponsor. A participant suffering an adverse event must receive appropriate care and safety measures until their clinical condition is resolved or stabilized, as described in the clinical protocol.

Upon becoming aware of an adverse event, the investigator must classify it according to causality, severity, intensity and expected/unexpected nature, as per ANNEX 1. And if the adverse event is considered serious, the investigator must inform the sponsor within 24 (twenty-four) hours from the date of becoming aware of the event.
event.

2r If the investigator becomes aware of an adverse event after the conclusion/end of the clinical trial, and there is suspicion of a possible causal relationship with the experimental drug, the sponsor must be informed as soon as possible. In these cases, the sponsor must have a monitoring plan in place so that late adverse events can be captured and become part of the safety profile of the experimental drug.

In addition to adverse events, other events that may impact the safety of clinical trial participants should also be considered in safety monitoring, as they may alter the benefit-risk balance of the investigational drug or clinical trial(s). Examples of relevant events include: a finding of risk for a patient population, such as the lack of efficacy of the investigational drug

used for the treatment of a life-threatening disease; an important safety finding observed in a recently completed nonclinical study (e.g.,
carcinogenicity); a temporary interruption/termination of a clinical trial in another country for safety reasons; recommendations of the Data Safety Monitoring Committee, when relevant to the safety of participants, relating, for example, to
an increase in the frequency or severity of an expected adverse reaction; among others.
In addition to the examples cited, this coordination also requests that communication be made information or security actions taken by other regulatory agencies or other
countries in which clinical development of the investigational drug is taking place.

The sponsor must continually reassess the risks and benefits of the clinical trial for participants, determining whether and when additional measures are necessary, including possible suspension of the study. In this case, the clinical trial in question should only continue after a reassessment of the benefit-risk balance that justifies its continuation, and after appropriate regulatory actions.

As part of safety monitoring, any pregnancy that occurs in a participant during a clinical trial must be followed until its outcome, and the baby must be monitored for the necessary period.

CL

6. SUSAR NOTIFICATION TO ANVISA

For regulatory submission purposes, notification of SUSARs occurring in clinical trials conducted in Brazilian territory is mandatory and must be carried out by the sponsor.

SUSAR is an adverse reaction that simultaneously meets the conditions of serious, unexpected and with a reasonable possibility of a causal relationship (i.e., suspected) with the experimental drug or active comparator.

ANNEX 2 presents a flowchart, which details the classification of the adverse event in terms of severity, causality and expected/unexpected nature, in order to assist in classifying the event as SUSAR.

“Related” causality is considered if, after an analysis of the relevant data, there is evidence of a “reasonable possibility” of a causal relationship for the individual case.

And the expression “reasonable possibility” of a causal relationship is intended to express, in general, that there are facts (evidence) or arguments that suggest a causal relationship.

If there is a divergence between the opinion of the investigator and the sponsor regarding the causal relationship, both opinions and justifications must be communicated to Anvisa, through notes inserted in the 'Notifier's Comments' field and in the 'Causality Assessment Comments' field, on the adverse reaction notification page in VigiMed.

As a joint action to notify Anvisa of SUSARs, the sponsor must also inform researchers involved in the clinical trial about SUSARs and take the necessary steps to update safety documents, such as the researcher's brochure, the drug leaflet (in the case of a registered drug) and other related documents. Until the Researcher's Handbook is updated, additional occurrences (monitoring) of SUSARs must be notified to Anvisa.

6.1. HOW TO NOTIFY

Notifications of SUSARs occurring in national territory must be carried out exclusively through the Vigimed system, in accordance with detailed guidelines described in the VigiMed Empresas User Manual - CLINICAL RESEARCH, and must contain at least the following criteria:

- Protocol number of the respective clinical trial and DEEC file
- Encoded participant identification
- Suspicious product under investigation
- Identifiable reporting source
- Event or result that can be identified as serious and unexpected

- Discussion of the existence of reasonable suspicion of a causal relationship.

When the case narrative is in English, a translation into Portuguese must be provided.

For more information, see the VigiMed Empresas User Manual – CLINICAL RESEARCH.

6.2. BREAKING THE BLIND

If there is a possibility that an event may be a SUSAR, the sponsor must break the blinding for notification to Anvisa, as well as to allow the updating of relevant documents, such as drug safety information in the researcher's booklet.

It is recommended that the sponsor unblind the treatment assignment only for the participant in question affected by the SUSAR and, whenever possible, preserve the blinding for those responsible for the analysis and interpretation of the study results and for those responsible for the continuity of the clinical trial, such as study managers, monitors and investigators. Therefore, these professionals should continue to receive SUSARs in a blind.

The investigator should only break the blinding of treatment allocation for safety reasons if breaking the blinding is relevant to the safety of the trial participant, when immediate action needs to be taken.

Unblinded information should be accessible only to those involved in communicating safety information to the Agency, to data safety monitoring boards (DSMBs) or to those performing ongoing safety assessments during the clinical trial. It is recommended that a dedicated team be established to perform all safety monitoring activities, including reporting SUSARs to Anvisa, in order to avoid unintentional breaking of blinding.

The integrity of the clinical trial may be compromised if blinding is systematically broken in the following situations:

- ÿ in clinical trials with participants suffering from diseases with high morbidity or mortality rates, in which the final efficacy assessment parameters may also be SUSAR;

  or

- ÿ when mortality or other serious consequences, which may potentially be notified as SUSAR, is the final efficacy assessment parameter;

In these or similar circumstances, the sponsor should highlight in the protocol those serious adverse events that should be treated as related to the disease and are not systematically subject to a break in blinding and reporting.

However, if these events are configured as a SUSAR, they must be notified to Anvisa.

For example, in a clinical trial designed to compare mortality between the test group and the control group, and the primary outcome is “death”, this event would generally not be

reported as SUSAR. However, if in such a trial, the death resulted from an anaphylactic reaction or hepatic necrosis temporally associated with the administration of the investigational drug, and not specifically to the disease or drug failure, in this case the event should be reported as SUSAR. That is, if there is a reasonable possibility of a causal relationship between the investigational drug and the event, it should be treated as SUSAR and should be reported.

7. SUBMISSION OF OTHER EAs AND CONDITIONS/EVENTS RELATED TO THE CLINICAL TRIAL PARTICIPANT SAFETY

Aggregated data on all adverse events, including those not categorized as serious, suspicious or unexpected, must be systematically evaluated by the sponsor or Independent Safety Monitoring Committee. The results of these evaluations must be submitted to Anvisa in the Experimental Drug Development Safety Update Report (DSUR) or whenever requested.

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

a) For regulatory submission purposes, these reports must be secondary electronic petitions linked to the DDCM process. Linking secondary petitions to the corresponding processes is essential for their analysis and traceability in Anvisa's electronic systems.

b) Petition subject 10825 – CLINICAL TRIALS – Report of Investigational Drug Development Safety Update;

c) All safety-related modifications to the DDCM that are considered non-substantial must be submitted to ANVISA as part of the safety update report for the development of the investigational drug;

d) Drug Development Safety Update Reports Experimental studies must be presented in the ICH *Development Safety Update Report* format. (DSUR), according to ICH E2F guide;

and) The sponsor must submit a single document containing data relevant to all dosage forms and strengths, all indications and study populations of the investigational medicinal product. If this is not possible, a justification must be presented in the introductory section of the DSUR report. For concomitantly administered medicinal products, the sponsor may submit a single DSUR covering the investigational medicinal product and other concomitantly administered therapies; or file separate reports for each investigational product.

For fixed-dose combinations, the sponsor must file a single DSUR covering all investigational products.

f) Drug Development Safety Update Reports Experimental must be sent to Anvisa annually, registered within a maximum period of

60 (sixty) calendar days, with the annual reference being the date of approval of the clinical trial in Brazil or the date determined in international development.

Relevant safety events that alter the benefit-risk balance of the experimental drug or clinical trial(s) exemplified in section 5 of this manual must be communicated to Anvisa as soon as possible, by means of an Addendum to the respective process (DDCM or DEEC) and, in parallel, by sending an e-mail to vigimed.pesquisa@anvisa.gov.br, communicating the petitioning of documents.

8. WHAT NOT TO NOTIFY TO COPEC

Adverse events occurring in phase IV studies and with registered drugs used as comparators or rescue drugs used previously or concomitantly in clinical trials must not be reported to COPEC. However, these occurrences must be reported to the competent technical area of Anvisa, in accordance with specific legislation.

It is important to note that medicines registered in Brazil, but in clinical development for some post-registration change, such as, for example, new therapeutic indication, new dosage, new population, among others, must follow the notification rules present in this manual.

9. CLINICAL TRIALS SUBMITTED UNDER RDC 09/2015

For clinical studies that are already underway and were approved under RDC 09/2015, notifications must be adapted to the requirements set out in RDC No. 945/2024.

10. TERMINOLOGY

We strongly recommend that SUSAR reports be made using MedDRA *(Medical Dictionary for Regulatory Activities)* terminology for coding adverse reactions and other medical terms such as cause of death, indication, test name, medical history and diagnosis.

Likewise, we recommend using the WHODrug dictionary to code drugs and active ingredients in notifications.

11. INDEPENDENT DATA MONITORING AND SECURITY COMMITTEE

It is desirable to establish an Independent Safety Monitoring Board (DSMB), regardless of the clinical phase. All clinical trials require safety monitoring, but not all trials require this monitoring to be performed by a committee. Therefore, the decision on the need to establish a DSMB should consider several factors, such as:

- ÿ clinical and scientific relevance for the clinical trial;
- ÿ potential benefits and acceptable risks for the protection of participants;
- ÿ type of population; ÿ
- clinical trial design, including objective(s) and outcome(s);

ÿ relevance of the committee to the integrity of the research.

The data collected by the sponsor must be submitted to the CMDS, if established, and the results of this assessment must be forwarded to Anvisa annually in the investigational drug development safety update report (DSUR) and whenever requested. If such an entity is not established, justification must be presented with information about the independent technical team that will be responsible for monitoring safety in the study protocol.

For the constitution, rules and functioning of the committee, we recommend reading the document Operational Guidelines for the Establishment and Functioning of Data Monitoring and Safety Committees, from the Ministry of Health, and other official documents issued by AREEs described in IN nº 338/2024 or its updates.

12. GLOSSARY

I – Equivalent Foreign Regulatory Authority (AREE): foreign regulatory authority or international entity that has regulatory practices aligned with those of Anvisa and that may be considered by Anvisa in a practice of regulatory trust *(Reliance);*

II - Independent Data and Safety Monitoring Committee (DSMC)
Independent Data Monitoring Committee, IDMC ou *Data and Safety Monitoring Board,* DSMB): independent committee, established by the sponsor, to evaluate, at defined intervals or as needed on an emergency basis, the progress of the clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, interrupt or suspend a trial;

III - Clinical trial: any interventional clinical research with human beings with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying the absorption, distribution, metabolism and excretion of the experimental drug to verify its safety and/or efficacy;

IV - Adverse Event (AE): any adverse medical occurrence in a clinical trial participant to whom an investigational product has been administered and which does not necessarily have a causal relationship with the treatment. An AE, therefore, is any unfavorable and unintended sign, for example, an abnormal laboratory finding, symptom or disease temporarily associated with the use of a drug, whether or not considered related to its use;

V - Serious Adverse Event (SAE) - any adverse medical occurrence with a product under investigation, occurring at any dose and resulting in death, risk of death, persistent or significant disability or incapacity, congenital anomaly/birth defect and situations requiring hospitalization or prolonged hospitalization;

VI - Experimental drug - pharmaceutical product under test, subject to the DDCM, to be used in the clinical trial, with the purpose of obtaining information for its registration or post-registration or renewal of registration;

VII - Notification: act of reporting the occurrence of an Adverse Reaction/Adverse Event of a medication to the health authority;

VIII - Product under investigation - product used as an experimental medicine, active comparator or placebo or any other product to be used in a clinical trial;

IX - 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;

X - Adverse Drug Reaction (ADR): harmful and unintentional response attributed to a drug, at doses normally used for prophylaxis, diagnosis or treatment of diseases or for the modification of a physiological function. In the context of clinical development, there are often no well-established doses and adverse drug reactions do not have a well-established causal relationship with the product and, therefore, are considered suspicious;

XI - Suspected Serious, Unexpected Adverse Reaction *(Serious, unexpected adverse reaction* - SUSAR) - It is an adverse reaction that simultaneously meets the conditions of serious, unexpected and with a reasonable possibility of a causal relationship, that is, suspected with the experimental drug and active comparator, as defined below:

a) serious: see Serious Adverse Event;

b) unexpected: a suspected adverse drug reaction (ADR) whose nature or severity is not consistent with the information available for the investigational product in the investigator's brochure (IB), Safety Information Summary (SIR) or package insert. The reaction may not be listed in the IB, SIR or package insert or may not be listed in the specificity or seriousness that was observed. The classification of unexpected is based on the perspective of previous observations, not on the basis of what can be anticipated from the pharmacological properties of a medicinal product;

c) suspicion: reasonable possibility that the experimental drug and active comparator caused the adverse reaction.

XII - VigiMed - Vigiflow system, used by the World Health Organization (WHO) to receive notifications of adverse events and provided by Uppsala Monitoring Centre (UMC) - a centre linked to the WHO.

13. BIBLIOGRAPHICAL REFERENCES

BRAZIL. National Health Surveillance Agency. Resolution RDC 945 of November 29, 2024. Provides guidelines and procedures for conducting clinical trials in the country with a view to the subsequent granting of drug registration. Available at: https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=RDC

&numeroAto=00000945&seqAto=000&valorAno=2024&orgao=RDC/DC/ANVISA/MS&codTi po=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true.

BRAZIL. National Health Surveillance Agency. Normative Instruction - IN No. 338, of November 29, 2024. Establishes, under the terms of the ANVISA Collegiate Board Resolution No. 945, of November 29, 2024, the list of Equivalent Foreign Regulatory Authorities (AREE) and details the criteria for the adoption of the optimized analysis procedure by reliance and by risk and complexity assessment of petitions for DDCM, DEEC, substantial modifications to the product under investigation and substantial amendments to the clinical protocol.

Available in: https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=INM& actNumber=00000338&actSeq=000&yearValue=2024&organization=DC/ANVISA/MS&typeCode=&de sItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true

BRAZIL. National Health Surveillance Agency. Normative Instruction - IN No. 345, of February 20, 2025. Amends Normative Instruction No. 338, of November 29, 2024.
Available in: https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=INM& actNumber=00000345&actSeq=000&yearValue=2025&organization=DC/ANVISA/MS&typeCode=&de sItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true

Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services National. Institutes of Health. National Cancer Institute. Disponível em: https://ctep.cancer.gov/ protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_re ference_8.5x11.pdf. Accessed on February 5, 2025.

European Union (EU) - Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC. Available at: < https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32014R0536 >.

FDA. Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans regulation to improve safety reporting in clinical trials.
Available at: <https://www.fda.gov/drugs/investigational-new-drug-ind-application/final-rule-investigational-new-drug-safety-reporting-requirements-human-drug-and-biological-products>. Accessed on December 23, 2024.

FDA. Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data https://www.fda.gov/ Disponível em: < information/search-fda-guidance-documents/ regulatory-Monitoring Committees. establishment-and-operation-clinical-trial-data-monitoring-committees>. Acesso em 24 de dez. 2024.

ICH Harmonised Tripartite Guideline - Clinical Safety Data Management: Definitions And Standards For Expedited Reporting - E2A (Step 4). Disponível em: < https://database.ich.org/sites/default/files/E2A_Guideline.pdf>

ICH Harmonised Tripartite Guideline - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B(R3). Disponível em: < https://ich.org/page/electronic-standards-estri>.

ICH Harmonised Tripartite - Guideline Development Safety Update Report - E2F. Available at < https://database.ich.org/sites/default/files/E2F_Guideline.pdf >.

ICH Harmonised Tripartite Guideline - Integrated Addendum To ICH E6(R2): Guideline For Good Practice E6(R2). Clinical Available at in: < https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>.

ICH Harmonised Tripartite Guideline - General Considerations For Clinical Studies - E8(R1). Available https://databaseich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf>.

ICH Harmonised Tripartite Guideline - A Selective Approach To Safety Data Collection In Specific Late-Stage Pre-Approval Or Post-Approval Clinical Trials - E19. Disponível: < https://database.ich.org/sites/default/files/ICH_E19_Guideline_Step4_2022_0826_0.pdf>.

ICH Final Concept Paper E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials Disponível https://database.ich.org/sites/default/files/ICH_E21_Final_Concept_Paper_2023_1106_MC E21 in:

Approved.pdf

HSA. Health Sciences Authority. CLINICAL TRIALS GUIDANCE EXPEDITED SAFETY REPORTING REQUIREMENTS FOR CLINICAL TRIALS. Government of Singapore. Disponível em: https://www.hsa.gov.sg/docs/default-source/hprg-io-ctb/hsa_gn-ioctb-10_safety_reporting.pdf?sfvrsn=6687bb4f_6

MINISTRY OF HEALTH, WORLD HEALTH ORGANIZATION. Operational Guidelines for the Establishment and Operation of Data Monitoring and Security Committees. at: <https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_operacionais_%20dados_segur Series A. Standards and Manuals Technicians

anca.pdf > Accessed on December 23, 2024.

National Health and Medical Research Council (NHMRC). Australian Government.
Department of Health Therapeutic Goods Administration. Safety monitoring and reporting in clinical trials involving therapeutic goods. Disponível em: <https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods>. Acesso em: 05/02/2025.

THE UPPSALA MONITORING CENTRE. WHO Collaborating Centre for International Drug Monitoring. Glossary of Terms in Pharmacovigilance. Available at: < https://who-umc.org/pharmacovigilance-communications/glossary/ >. Accessed on December 23, 2024.

THE UPPSALA MONITORING CENTRE. WHO Collaborating Centre for International Drug Monitoring. The use of the WHO-UMC system for standardised case causality assessment.
Available at https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf >. Accessed on December 23, 2024.

WORLD HEALTH ORGANIZATION. WHO Collaborating Centre for International Drug Monitoring. Safety Monitoring of Medicinal Products: Guidelines for setting up and running a Pharmacovigilance Centre. Geneva, World Health Organization, 2000. Disponível em: < https://who-umc.org/media/1703/24747.pdf > Acesso em 23 de dez. 2024.

14. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st Edition	Initial version	
2nd Edition	Updates throughout the document	Amendment of RDC 09/2015 to RDC 945/2024 and inclusion of IN 338/2024 and Law 14.874/2024
2nd Edition	Update of the Acronym section	Inclusion of new acronyms
	Introduction section update	Inclusion of information on the scope of clinical research on and importance for the development of new medicines and biological products. Inclusion of information about the new clinical research resolution, RDC nº 945/2024
2nd Edition	Objective section update	Section Relocation - Purpose and change of reporting of Adverse Events serious (possible, probable or definite causality) to Suspicion Reaction Adversa Grave Inesperada *(suspected unexpected serious adverse reactions* – SUSARs)
2nd Edition	Update of the Legal Basis section	Relocation of the Legal Basis section and update with Law 14,874/2024 and RDC No. 945/2024

2nd Edition	Security Monitoring section update	Update with information that enables and guides companies on ways to make monitoring the drug safety profile efficient and appropriate. Inclusion of guidelines on what and how to communicate relevant events to Anvisa has security
2nd Edition	Update to the AE Reporting section The Adverse Event Reporting section was changed to	SUSAR Reporting to Anvisa, reflecting the new approach proposed by RDC No. 945/2024 and restructured to include subsections How to Report and Unblinding. The system for receiving SUSAR reports, as currently VigiMed, was also updated. The requirement for the respective translation of the case narrative into Portuguese was included when it is in English.
2nd Edition	Traceability Section	The Traceability section has been deleted
2nd Edition	Update to the Submission of other EAs section	The Submission of Other AEs (Safety Update Report) section has been changed to Submission of AEs Conditions/Events related to Clinical Trial Participants safety. and Inclusion of information on how to report relevant events you security

2nd Edition	Section - When Not to Notify the Event Adverse to Anvisa	The When Not section Report Adverse Event To Anvisa it was changed to What not to Notify to COPEC. Content was adequate
2nd Edition	Inclusion of Section 9	Inclusion of the section Clinical Trials Submitted under RDC No. 09/2015
2nd Edition	Terminology Section Update	Update of the Terminology section with the recommendation to use the MedDRA dictionary for coding adverse reactions and other medical terms such as cause of death, indication, name of tests, medical history diagnosis; and WHODrug for coding drugs and active ingredients in notifications and
2nd Edition	Deletion of the Gradation Section Intensity Qualifier To Health Conditions (WHO)	The Qualifying Intensity Grading for Health Conditions (WHO) section has been deleted and the content of this section has been incorporated into Annex 1.
2nd Edition	Committee Section Update Independent Monitoring of Data and Security	The Independent Data Monitoring Committee Section and of Security was changed removing the requirement of a Committee Independent of Monitoring Safety for phase III studies and making it optional, through evaluation of factors that justify the establishment or not of a CMDS, regardless of the clinical phase. In addition, the request to send the results of the CMDS evaluation to Anvisa was included

		annually in the investigational drug development safety update report (DSUR) and whenever requested
2nd Edition	Update of the Glossary and Bibliographic References	Glossary update and Bibliographic References
2nd Edition	Flowchart Deletion	Deletion of Flowchart Event Notification Adverse Events in Trials Clinical
2nd Edition	Attachment deletion	Deleting the System attachment WHO-UMC for standardized assessment of causality
2nd Edition	Inclusion of new annex	Inclusion of Annex 1 – Event Classification Adverse effects for guidance on the classification of adverse events
2nd Edition	Inclusion of new annex	Inclusion of Annex 2 - Flowchart for Event Characterization Adverse Events for Notification to Anvisa

ANNEXES

ANNEX 1 - CLASSIFICATION OF ADVERSE EVENTS

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or illness temporally associated with the use of a medical treatment or procedure, which may or may not be considered related to the medical treatment or procedure. An AE is a term that uniquely represents a specific event used for medical documentation and scientific analysis.

After becoming aware of the occurrence of an adverse event, the investigator must classify it according to the following parameters:

1. Regarding the intensity

Intensity refers to the clinical impact of the event on the participant's life. During the case narrative, AEs are listed, accompanied by a description of intensity.

The term *"severe"* will be translated into Portuguese as "severo" and used to describe the severity of a specific event (as in mild, moderate or severe myocardial infarction) – the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as *"serious",* which is based on patient/event outcome or action criteria generally associated with events that pose a threat to the patient's life or function. Seriousness *serves* as a guide to define regulatory reporting obligations.

Among the criteria that can be used for intensity classification, but not limited to this example, is the CTCAE (Common Terminology Criteria for Adverse Events), mainly used in clinical studies designed to evaluate antineoplastics, which is subdivided into a classification scale that varies between 1 and 5:

Grade 1: Mild; asymptomatic or mild symptoms; only clinical or diagnostic observations; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limits age-appropriate instrumental activities of daily living (ADL).

Grade 3: Serious/severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limits self-care activities (self-care ADL).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

2. Regarding gravity

For regulatory purposes, the translation of the English term *"serious"* is considered as "grave", which expresses serious adverse reaction and serious adverse event.

A Serious Adverse Event is considered any adverse medical occurrence with a product under investigation, occurring at any dose and resulting in any of the following outcomes:

a) death;

b) risk of death;

c) persistent or significant incapacity/disability;

d) requires hospital admission or prolongs hospitalization;

e) congenital anomaly or birth defect;

f) clinically significant event.

The term "life-threatening" in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time it occurred. It does not apply to events that, hypothetically, could have caused death if they had been more serious.

Medical and scientific judgment should be used to decide whether immediate reporting is appropriate for important or clinically significant medical events, such as events that may not be immediately life-threatening or result in death or hospitalization, but may place the patient at risk or may require intervention to prevent a serious adverse event. Accordingly, these events should generally be considered

graves.

3. Regarding causality

To assess the causal relationship, documents internationally recognized by equivalent AREEs may be used, in accordance with IN No. 338/2024 or its updates.
However, the method or classification used must be described in the clinical trial protocol.

It is important to emphasize that the existence of a rationale for assessing causality is important to standardize parameters that allow impartiality, reproducibility, as well as parameterization of assessments among all investigators of the clinical trial. Investigators and Sponsors must work together to define the causality of the event.

adverse.

When assessing causality, several factors may be considered to decide whether there is a "reasonable possibility" that an AE was caused by the investigational drug, such as
as:

• Period of Exposure to the suspected drug/temporality: assess whether the participant received the suspected drug and whether there is a reasonable temporal relationship with the administration of the suspected drug;

• Consistency with known drug profile/mechanism of action: understand whether the AE was consistent with prior knowledge of the suspected drug (pharmacology, toxicology and other non-clinical studies) or drugs of the same pharmacological class.

• Available data on drug suspension and rechallenge/dechallenge: assess whether the AE was resolved or whether the participant improved with drug suspension or resolution of the AE

• Alternative causes: check that the AE cannot be reasonably explained by another aetiology, underlying disease/co-morbidities, other medications or environmental factors.

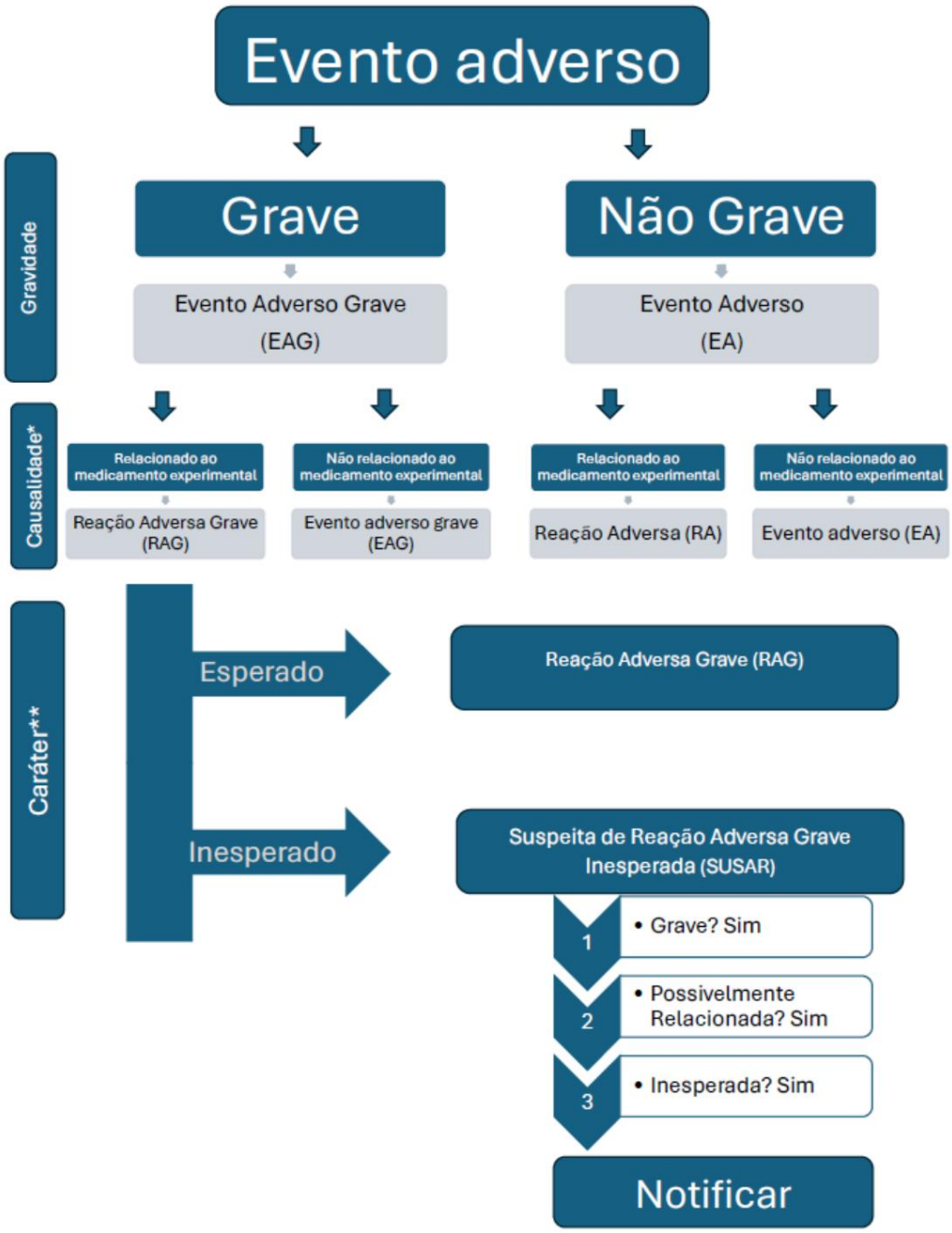
• Laboratory tests: if a specific laboratory investigation has been carried out, evaluate if there is confirmation of the causal relationship.

4. Regarding the 'expected' or 'unexpected' character

An adverse reaction is understood to be unexpected when its nature or severity is not consistent with the Reference Safety Information (RSI) contained in the Investigator's Brochure or equivalent document containing the drug information.

In this way, an expected adverse reaction can be understood as known and associated with the treatment/medication to which the participant was exposed and which is part of the Researcher's Brochure or another equivalent document, such as the package insert, in the case of already registered medications.

ANNEX 2 - FLOWCHART FOR CHARACTERIZATION OF ADVERSE EVENTS FOR NOTIFICATION TO ANVISA



Fonte: Adaptado do NHMRC - Safety monitoring and reporting in clinical trials involving therapeutic goods.
*Related as a reasonable possibility of a causal relationship or defined, if the causal relationship has already been proven
**Assessed using baseline safety information from the study [current Investigator's Brochure or Product Information (package insert)]