Söğütözü Mahallesi, 2176. Street No:5 06520 Çankaya/ANKARA
Telephone No: (0 312) 218 30 00 Fax No: (0 312) 218 34 60
e-Mail: halkla.iliskiler@titck.gov.tr Website:
https://www.titck.gov.tr
Kep Address: titck@hs01.kep.tr

GUIDELINE ON SAFETY REPORTING IN CLINICAL TRIALS.

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1. PURPOSE This guideline has been prepared for the purpose of determining the procedures and principles regarding the systematic monitoring of adverse events or reactions occurring in clinical trials of medicinal products for human use conducted in our country, the collection, verification, recording, unblinding, assessment and archiving of information on this matter, as well as the management and reporting thereof. 2. SCOPE It covers matters relating to safety reporting in clinical trials within the scope of the Regulation on Clinical Trials of Medicinal Products for Human Use, published in the Official Gazette No. 32203 dated 27 May 2023. 3. LEGAL BASIS It has been prepared based on the Regulation on Clinical Trials of Medicinal Products for Human Use, published in the Official Gazette No. 32203 dated 27 May 2023. 4. DEFINITIONS AND ABBREVIATIONS EU: the European Union, Investigational product: a medicinal product for human use that is tested or used as a reference in a clinical trial, including placebo, Unexpected serious adverse reaction: an adverse reaction the nature, severity or outcome of which is not consistent with the reference safety information of the product, Serious adverse event: all serious unwanted medical events occurring in a volunteer participating in the clinical trial, whether or not considered to have a causal relationship with the treatment administered, Serious adverse reaction: an adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly/birth defect, DSUR (Development Safety Update Report): the development safety update report submitted once a year throughout the clinical trial or upon request, containing all safety information emerging during the reporting period, ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use): the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH E2B(R3) (Electronic Transmission of Individual Case Safety Reports (ICSRs)): the electronic transmission of individual case safety reports (ICSRs),

Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), MedDRA (Medical Dictionary for Regulatory Activities): the Medical Dictionary for Regulatory Activities, PT (Preferred Term): the Preferred Term, RSI (Reference Safety Information): the Reference Safety Information, SUSAR (Suspected Unexpected Serious Adverse Reaction): any serious adverse reaction the nature or severity of which is not consistent with the reference safety information of the investigational product (suspected unexpected serious adverse reaction), Auxiliary medicinal product for human use: a medicinal product for human use licensed in Türkiye which is not a clinical trial investigational product but is used in accordance with the requirements or needs set out in the clinical trial protocol, Regulation: the Regulation on Clinical Trials of Medicinal Products for Human

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Use, published in the Official Gazette No. 32203 dated 27 May 2023, shall mean. In addition to these definitions, the definitions specified in the Regulation on Clinical Trials of Medicinal Products for Human Use and in the Good Clinical Practice Guideline shall apply. 5. RESPONSIBILITIES 5.1. The responsibilities of the investigator or sponsor regarding safety reporting are explained in the Good Clinical Practice Guideline and the relevant legislation. 5.2. The sponsor is responsible for the safety assessment of the investigational product. 5.3. In circumstances that may adversely affect the health of a volunteer or the conduct of the trial, or that may lead the Agency to modify its authorisation for the continuation of the trial, the sponsor shall promptly inform all investigators concerned by the trial, the coordinator, the administrative responsible person, the relevant ethics committee and the Agency. 5.4. The sponsor shall establish systems and written standard operating procedures that ensure the necessary quality standards at every stage related to case documentation, data collection, validation, assessment, archiving and reporting. 5.5. The procedures and principles regarding reporting related to auxiliary medicinal products for human use are set out in the relevant guideline. The said processes are presented schematically in Annex-1 of this Guideline.

6. RECORDING, ASSESSMENT AND REPORTING OF ADVERSE EVENTS OR REACTIONS 6.1. The entry of adverse events into the case report form covers the identification and processing of the data in each case, the identification and processing of alerts requiring special attention, and the review of all other cases. 6.2. Case report processing concerns the assessment of data in individual cases, the identification of individual cases requiring special attention, the recognition and processing of alerts, and the processing of other data for cases in aggregate. 6.3. Individual adverse events shall be assessed by the investigator. This assessment shall also include an assessment of the severity of the adverse event and of its causal relationship with the investigational product or concomitant therapies. 6.4. Records of all adverse events reported by the investigator to the sponsor shall be kept in detail by the sponsor. These records shall be submitted to the Agency and the ethics committee upon request. 6.5. The sponsor shall assess the severity, causality, and expectedness or unexpectedness of all adverse events or reactions reported to it by the investigator. 6.6. All adverse events considered by the investigator or the sponsor to have a reasonable causal relationship with the investigational product shall be defined as adverse reactions. 6.7. Where the reporting investigator does not provide information on causality, the sponsor shall encourage the investigator to express an opinion on this matter. 6.8. The causality assessment made by the investigator shall not be rejected by the sponsor. The causality assessment made by the sponsor shall also be indicated in the report. If the sponsor does not agree with the investigator's causality assessment, both the investigator's and the sponsor's opinions shall be clearly stated in the report. 6.9. The expectedness of an adverse reaction is assessed according to the RSI provided by the sponsor. 6.10. The RSI is included in the summary of product characteristics or the investigator's brochure. The section of the application cover letter submitted to the Agency and the ethics committee in which the RSI is located shall be indicated.

6.11. In assessing the expectedness of an adverse reaction, it shall be considered whether the event presents a significant difference in terms of specificity, an increase in frequency, or severity compared to known and already documented serious adverse reactions, or whether it provides additional information. 6.12. The expectedness assessment is made on the basis of events previously observed with the active substance, not on the basis of the expected pharmacological effects of the investigational medicinal product or events related to the participant's disease. 6.13. The RSI may change during the clinical trial. For the purpose of SUSAR reporting, the version of the RSI in force at the date the adverse reaction occurred shall be taken into account. Changes made to the RSI may affect the number of adverse reactions to be reported as SUSARs. 6.14. Where the investigator has provided information regarding expectedness, this information shall be taken into account by the sponsor. 6.15. The investigator is obligated to report to the sponsor all serious adverse events occurring in participants taking part in the clinical trial. Unless otherwise specified in the protocol or extended follow-up is requested with justification by the Agency or the relevant

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ethics committee, the investigator is not required to actively follow up participants for adverse events after completion of the trial. 6.16. The investigator who becomes aware of serious adverse events occurring in a participant after completion of the trial shall report these events to the sponsor. 6.17. Except for serious adverse events for which the protocol states that immediate reporting is not required, the investigator shall report serious adverse events to the sponsor no later than 24 (twenty-four) hours from the moment of becoming aware of them. 6.18. Adverse events or abnormal laboratory findings defined in the protocol as critical for safety assessments shall be reported to the sponsor within the time limits specified in the protocol and the relevant legislation, in accordance with the reporting requirements. 6.19. The investigator is obliged to submit any requested information (in particular in the event of the death of a participant) to the relevant ethics committee, the Agency, and the sponsor. 6.20. It is the responsibility of the sponsor to notify the relevant ethics committee and the Agency of SUSARs arising during the trial that were fatal or life-threatening, no later than 7 (seven) days from the moment the said information reaches the sponsor; and of SUSARs that were not fatal or life-threatening, no later than 15 (fifteen) days following receipt of initial information.

6.21. SUSARs assessed at initial reporting as not fatal or life-threatening but subsequently found to be fatal or life-threatening during the follow-up period shall also be notified to the relevant ethics committee and the Agency within 7 (seven) days at the latest. 6.22. The principles of confidentiality shall always be observed in the reporting and recording processes, and the provisions of the legislation in force on data protection shall be complied with. 6.23. The sponsor shall report SUSARs in accordance with the following cases, specifying the full name of the trial, the trial code, the protocol code, the participant code, the trial site where the event occurred, and, if available, the reporting number of the final report: 6.23.1. All SUSARs related to the investigational medicinal product that occurred in our country in the relevant trial shall be reported individually in XML format in compliance with the ICH E2B (R3) electronic transmission standard. The requirements for the XML file to be reported and the checks during the application process are set out in Annex-2. 6.23.2. All SUSARs related to the investigational medicinal product that occurred abroad shall be reported as 6-monthly line listings in accordance with Annex-3. 6.24. Safety issues that could alter the current benefit-risk assessment of the investigational medicinal product or that could necessitate changes in the administration of the investigational medicinal product or in the conduct of the trial shall also be reported. For example: - A clinically important increase in frequency or qualitative change of an expected serious adverse reaction, - Post-trial SUSARs arising after the participant's completion of the clinical trial and reported by the investigator to the sponsor, - New events developing in connection with the conduct of the trial or the development of the investigational medicinal product with the potential to affect participant safety, - A serious adverse event that may be related to trial methods and may change the conduct of the trial, - Causing serious risk to the participant population, for example lack of efficacy of an investigational medicinal product used in the treatment of a life-threatening disease, - The existence of a major safety finding from newly completed animal studies, - All safety findings that led to the suspension or temporary suspension of trials conducted by the same sponsor with the same investigational medicinal product in another country, - If any, recommendations of the independent data monitoring committee applicable for the safety of participants. 6.25. Expedited reporting is generally not required for adverse reactions that are not serious. 6.26. The sponsor shall inform all investigators participating in the trial of information regarding SUSARs that may adversely affect participant safety.

6.27. The investigator shall report to the sponsor information on SUSARs that may affect the safety of participants. 6.28. The provisions of the Guideline on Auxiliary Medicinal Products for Human Use shall apply to safety reports related to auxiliary medicinal products for human use. 6.29. Where SUSARs relate to placebo (e.g., a reaction to an excipient), the reporting of such cases is the responsibility of the sponsor. 6.30. The sponsor shall inform the Agency within the timeframes specified in the relevant legislation after obtaining the initial information meeting the

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minimum reporting criteria. 6.31. If the sponsor has not been able to access all data belonging to the participant (other than mandatory information) at the time of the initial report, the sponsor shall submit the follow-up report containing additional information to the Agency within 8 (eight) days from the moment all information reaches the sponsor. 6.32. In each case, follow-up information shall be tracked and the report shall be completed as rapidly as possible. Follow-up information shall be submitted to the relevant ethics committee and the Agency as soon as possible after it reaches the sponsor. 6.33. The sponsor shall report all notifications and reports on safety issues to the relevant ethics committee and the Agency within the timeframes specified in the relevant legislation. Additional follow-up information shall also be provided as soon as possible. The sponsor shall inform all investigators concerned. 6.34. Information related to the final evaluation of an adverse reaction report may not be completed within the timeframe in which reporting must be made. Due to the relevant legislation, initial reports must be submitted within the specified timeframes as soon as the minimum criteria set out below are met: 6.34.1. TİTCK code 6.34.2. Clinical trial protocol code 6.34.3. "Coded" identification data of the participant 6.34.4. Clear identification data of the reporting person 6.34.5. SUSAR 6.34.6. Suspected investigational product (including active substance name/code) 6.34.7. Causality assessment 6.34.8. Unique code of the safety report 6.34.9. Date on which the initial information was received from the primary source 6.34.10. Date on which the most recent information was received 6.34.11. Universal unique case identification number 6.34.12. Information regarding the sender 6.35. If information is missing at the time of the initial report, all appropriate information necessary for an adequate causality analysis shall be requested from the person writing the report or obtained from other available sources. The sponsor shall report further information in the form of a follow-up report after it has been received. Subsequently, follow-ups belonging to the participant shall be submitted to the Agency as follow-up reports. 6.36. Notifications to the Agency shall be made through the electronic application system.

6.37. Details regarding the application submission are specified in the Guideline on Clinical Trial Applications Submitted to the Turkish Medicines and Medical Devices Agency Clinical Trials Department. A sample cover letter for the submission of these reports is available on the official website of the Agency. 6.38. Any change that increases the risk to participants and any new circumstance that may adversely affect the safety of participants or the conduct of the trial shall be submitted to the relevant ethics committee and the Agency as rapidly as possible, not exceeding 7 (seven) days. 6.39. Each SUSAR report (initial report, follow-up report, and follow-up tracking report) shall contain information enabling the determination of whether the report is the same (recurring). The code of the participant in whom the SUSAR occurred, the worldwide unique case identification number belonging to the participant, and the number of SUSARs must be unique for the same trial, regardless of when they occurred. However, in circumstances requiring a change, the sponsor shall notify the relevant ethics committee and the Agency in the cover letter together with the justification for the change. If the sponsor becomes aware that duplicate reporting (duplication) has been made, this shall be communicated appropriately to the relevant ethics committee and the Agency. 6.40. The sponsor shall inform all investigators concerned of findings that may adversely affect the safety of participants. 6.41. In the case of blinded/masked trials, the line listing shall contain data on all SUSARs, regardless of the investigational product administered. Thus, where possible and appropriate, blinding is maintained and the risk of informing investigators of the identity of the investigational product is avoided. 6.42. If a significant safety issue is identified in the review of an individual case report or aggregated data, the sponsor shall inform all investigators as rapidly as possible. Safety issues that have an impact on the course of the clinical trial, including the temporary halt of the trial or safety-related amendments to the trial protocol, or on the development programme shall also be reported to the investigators. 7. PREPARATION OF REPORTS OF ADVERSE EVENTS OR REACTIONS IN BLINDED/MASKED TRIALS 7.1. Maintaining the blinding for all participants in the trial until the final analysis of the trial is generally desirable. However, in the case of an unexpected serious adverse

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reaction, the sponsor may break the blinding for that participant only, even if the investigator has not broken the blinding. 7.2. If possible, the blinding of personnel who will perform the data analysis and evaluate the results upon completion of the trial should be maintained. 7.3. The breaking of the blinding for a single participant by the investigator may be performed if it is related to participant safety. 7.4. In a blinded/masked trial, the severity of the adverse event, its causal relationship, and its expected or unexpected status shall be assessed on the assumption that the investigational product caused the reaction in question. If an event is potentially a SUSAR, the sponsor

by the unblinding is removed only for that volunteer. If, following the unblinding, the event turns out to be a SUSAR, the notification rules for SUSAR reporting apply. 7.5. Following unblinding, the reporting of SUSARs related to placebo is the responsibility of the sponsor. 8. ARRANGEMENT OF REPORTS OF ADVERSE EVENTS OR REACTIONS IN CLINICAL TRIALS RELATED TO A DISEASE WITH HIGH MORBIDITY OR MORTALITY 8.1. In clinical trials related to a disease with high morbidity or mortality, an efficacy endpoint or a death may be reported as an adverse reaction, and unblinding may jeopardize the integrity of the trial. In such cases, provided that the Agency and the relevant ethics committee are informed in advance and approval is granted by the Agency and the relevant ethics committee, adverse reactions may be accepted as related to the disease and not unblinding the trial may be acceptable. The methods for reporting such adverse reactions must be clearly defined in the protocol. 8.2. In clinical trials related to a disease with high morbidity or mortality, sponsors are recommended to establish an independent data monitoring committee for the purpose of regularly reviewing the safety data of the ongoing trial and providing advice on whether to continue or modify the trial. 8.3. The structure and operation of the independent data monitoring committee must be described in the trial protocol. The opinion and recommendations of the independent data monitoring committee must be reported by the sponsor to the relevant ethics committee and the Agency in the form of a report. However, SUSARs that are not efficacy endpoints in the same trial must be reported as required. 9. DEVELOPMENT SAFETY UPDATE REPORTS 9.1. In addition to adverse event or reaction reports, the sponsor must report, once a year throughout the trial or upon request, all available new safety information emerging during the reporting period to the relevant ethics committee and the Agency, using the cover letter template published on the Agency's official website. 9.2. Where the sponsor conducts more than one trial with the same investigational product, the DSUR must contain a brief overall analysis of the safety profile of the investigational product based on the experience obtained from all trials conducted by the sponsor and all available data. 9.3. The reference safety information in effect at the beginning of the reporting period must be submitted as an annex to the report. 9.4. The reference safety information in effect at the beginning of the reporting period is taken into account as the reference safety information throughout the reporting period. 9.5. In case significant changes are made to the reference safety information during the reporting period, these must be presented in a list in the DSUR. 9.6. The DSUR must consist of three sections: 9.6.1. Section 1: A report on the safety of the volunteers in the relevant trial;

9.6.1.1. The sponsor must present, together with its own opinion, a brief safety analysis and benefit-risk assessment of the relevant clinical trial, report all new findings (not previously included in the investigator's brochure or in the SmPC/PIL) known to the sponsor concerning the safety of treatments with the investigational product, and present an analysis assessing their impact on the volunteers. If available, the opinion and recommendations of the independent data monitoring committee must also be appended to the report. 9.6.1.2. The analysis of the possible effects for the clinical trial population must be completed, and at the same time, the safety profile of the investigational product and its possible effects on the volunteers must also be analyzed, taking into account all available safety data. The following points must be taken into account during the analysis: - Relationship to the dose and duration of treatment, - Reversibility of the effect, - Occurrence of previously undefined toxicity in volunteers, - Increase in the frequency of

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toxicity, - Overdose and its treatment, - Interactions or other related risk factors, - Any specific safety issues related to special populations such as the elderly, children, or any other risk group, - Positive and negative experiences during pregnancy or breastfeeding, - Misuse, - Risks that may be related to the diagnostic and investigative methods used in the clinical trial, - Risks that may be associated with inadequate quality of the investigational product. 9.6.1.3. The results obtained from non-clinical trials related to the investigational products and other experiences that may affect the safety of the volunteers must also be evaluated in the report. 9.6.1.4. Measures taken in the past or currently proposed to minimize the identified risks must also be detailed. 9.6.1.5. A detailed justification must be provided as to whether it is necessary to modify or update the protocol, the informed consent form (ICF), and the investigator's brochure. However, this report does not substitute for a request for a protocol modification. 9.6.1.6. A benefit-risk assessment of the clinical trial must be performed. 9.6.2. Section 2: A line listing of all SUSARs that occurred in the relevant trial; 9.6.2.1. The annual report must contain a line listing of all SUSAR reports reported during the trial. 9.6.2.2. The line listing contains key information. It is not required to individually contain details of the cases. 9.6.2.3. Regardless of how many adverse reaction reports have been submitted for a case, it must include each volunteer only once. That is, if more than one adverse reaction has occurred in a volunteer,

all of these should be mentioned; however, the adverse reactions should be ranked in terms of severity (finding, symptom or diagnosis) according to the sponsor's assessment. It is possible for the same participant to experience different adverse reactions in different circumstances. Such experiences should be handled as separate reports. In such cases, the same participant may appear more than once in a line listing. This should be indicated in the line listings. 9.6.2.4. Cases should be presented in tabular form by body system (standard system organ classification scheme). 9.6.2.5. There should be one list for each trial; however, separate lists should be submitted for the auxiliary medicinal product for human use or placebo, or for other appropriate and relevant reasons (e.g. cases where different formulations, indications or routes of administration are examined in the same trial). 9.6.3. Section 3: Cumulative summary tabulation of suspected serious adverse reactions that occurred in the relevant trial (provided in Annex-4); 9.6.3.1. In addition to the line listings of individual cases presented in Section 2, summary tabulations of all serious adverse reactions observed during the trial should be presented in a manner that allows an overall evaluation of the trial. In these tabulations, serious adverse reaction terms relating to findings, symptoms or diagnoses should be presented. Where the number of cases is low, presentation in narrative form is more appropriate. 9.6.3.2. The cumulative summary tabulations should indicate the number of reports relating to: - Each body system, - Each adverse reaction term, - If applicable, each treatment arm (investigational product, comparator product or placebo). 9.6.3.3. Unexpected adverse reaction terms should be explicitly defined in the table. 9.7. The reporting period for the DSUR begins on the date of the first authorisation granted by the Agency for the clinical trial. The data lock point should be determined on the basis of the authorisation date of the clinical trial conducted in our country with the relevant investigational product. 9.8. Data from this date up to the end of the first year should be included in the Development Safety Update Report (DSUR). The sponsor must submit these reports within 60 (sixty) days after the data lock point. 9.9. Even if the sponsor is conducting more than one clinical trial with the same investigational product, it must prepare safety reports covering the necessary information on all of these trials separately for each trial. 9.10. The safety report for the first administration to humans, bioequivalence and bioavailability studies, and short-term metabolism or pharmacokinetic trials shall be notified within 90 (ninety) days after completion of the trial. This report must include, as a minimum, the line listing (Annex-5), if applicable the cumulative summary tabulations, and an explanation regarding participant safety. 10. ENTRY INTO FORCE This Guideline enters into force on the date of its approval.

11. EXECUTION The President of the Agency executes the provisions of this Guideline.

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ANNEX-1: SAFETY NOTIFICATION WORKFLOW DIAGRAM

ANNEX-2: SUSAR NOTIFICATION SUBMODULE – XML VALIDATION PROCESS The XML validation process applied in the SUSAR Notification Submodule is carried out within the framework of a stepwise structure, as also shown in the user interface. Following the upload of an XML file to the system, the validation process is carried out by following the steps below:

1. XSD Schema Validation The technical compliance of the XML file with the ICH E2B(R3) schema is checked. 2. ICH Field Mandatory and Repetition Checks Compliance with the mandatory (mandatory / conditional mandatory) and repetition (cardinality) rules of the fields defined in the ICH standard is verified. 3. ICH Content (Business Rule) Checks The compliance of field values with the ICH E2B(R3) business rules (as specified in the guideline entitled "Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification") is checked. 4. TİTCK Business Rules In addition to the ICH E2B(R3) business rules, TİTCK business rules are applied. These rules are evaluated under two main headings: 4.1. General TİTCK Rules 4.1.1. Field C.1.3 must only take the value "2 = Report from study". 4.1.2. Field C.1.7 must be "true". 4.1.3. Field C.1.3.1 must only be "1 = Pharmaceutical Company". 4.1.4. Field C.2.r.3 must be a valid country code. 4.1.5. Field C.2.r.5 must only be "Primary". 4.1.6. At least one of the E.i.3.2 (seriousness criteria) fields must be "true". 4.1.7. The Receiver ID to be designated for the XML file must be set as "TITCK". 4.2. EU Causality Rules The rules concerning the EU causality assessment are applied within the scope of the TİTCK business rules as follows: 4.2.1. Source of Assessment can only take the following values: 4.2.1.1. 1 = Investigator 4.2.1.2. 2 = Sponsor 4.2.2. Method of Assessment must only be "1". 4.2.3. Result of Assessment can only be "1" or "2". 4.2.4. If the Method of Assessment value is "1": 4.2.4.1. The Source of Assessment and Result of Assessment fields are mandatory. 4.2.5. If the case contains a suspect/interacting drug (G.k.1 = 1 or 3): 4.2.5.1. There must be at least one EU causality assessment. 4.3. Follow-up Notification Approach

For XML files considered as follow-up notifications, validation is performed within the scope of the schema, ICH E2B(R3) and TİTCK business rules. If an Amendment or Nullification is to be made in follow-up notifications, the C.1.11.1 Report Nullification / Amendment and C.1.11.2 Reason for Nullification / Amendment fields must be completed appropriately.

ANNEX-3: CONTENT OF THE LINE LISTING The line listing should contain the following information for each case: 1. Protocol code and, if available, TİTCK Trial Code, 2. Participant code, 3. Sponsor's adverse reaction case reference number (Case-Identification Number), 4. Age and sex of the participant, 5. Treatment group; if the blinding has not been broken, it is identified as "blinded/masked". 6. Daily dose of the investigational product (dosage form and route of administration), 7. Onset date of the adverse reaction, 8. Treatment dates, 9. Adverse reaction(s); must be coded at the preferred term level using MedDRA terminology. 10. Outcome of the participant (recovery, sequelae, death, etc.). In this field, the consequences of the reaction(s) on the participant should be specified. In case of more than one reaction, the most severe outcome should be taken as the basis. 11. Comments (e.g. causality assessment in cases where the views of the sponsor and the reporter differ; concomitantly used drugs considered to have played a role in the reactions, directly or through interaction; the indication treated with the suspect drug(s); the results of dechallenge/rechallenge, if available), 12. Annex-5 contains an example of the line listing headings.

ANNEX-4: EXAMPLE OF A CUMULATIVE SUMMARY TABLE Body system/ADR term Active Treatment (Verum) Placebo Blinded Central Nervous System

Hallucinations* Confusion*

Subtotal

2**

1 3

1 3

0 0

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* Indicates an example of a SUSAR. **Indicates the number of reports according to terms (findings, symptoms and diagnoses).

ANNEX-5: EXAMPLE OF A LINE LISTING

Protocol Code Case Reference Number / Volunteer Code* Country
Sex
Age Serious Adverse Reaction** Outcome
Onset Date**
Time Elapsed to Onset** Suspected Medication Daily Dose
Route of Administration
Formulation Treatment Dates
Treatment Duration Comments
* Trial/site/volunteer ** Only "Primary" Serious Adverse Reaction
Cardiovascular System
Subtotal

REVISION HISTORY Revision No Revision Date Rationale and Explanations 00 28.01.2009 Updated prior to the establishment of the quality management system. 01 20.04.2009 Updated prior to the establishment of the quality management system. 02 22.10.2009 Updated prior to the establishment of the quality management system. 03 16.03.2010 Updated prior to the establishment of the quality management system. 04 24.12.2010 Updated prior to the establishment of the quality management system. 05 05.09.2011 Updated prior to the establishment of the quality management system. 06 19.04.2013 Updated prior to the establishment of the quality management system. 07 10.05.2013 Updated prior to the establishment of the quality management system. 08 06.08.2014 Updated prior to the establishment of the quality management system. 09 13.11.2015 Updated prior to the establishment of the quality management system. 10 01.02.2024 Updated due to a change in the Regulation. 11 26.04.2024 Updated due to the revision of the safety reporting workflow diagram included in the Annex. 12 15.04.2025 Updates/additions were made to the definitions (Section 3) and Section 5 regarding the reporting of serious adverse events with fatal outcome. 13 15.05.2026 In line with the national SUSAR module, updates were made in Sections 1, 3, 4, 6 and 7 and in Annex-1, Annex-2, Annex-3 and Annex-5 in order to ensure compliance with ICH E2B(R3) and Regulation (EU) No 536/2014 on clinical trials on human subjects.

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