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**Detailed guidance on the European database  
of Suspected Unexpected Serious Adverse  
Reactions  
(Eudravigilance – Clinical Trial Module)**

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## **1 Introduction**

European regulatory authorities require a database in order to provide each of them with an overview of the suspected unexpected serious adverse reactions (SUSARs) linked to investigational medicinal products used in clinical trials being conducted in the community, and in the respective Member States. This database is needed to facilitate the review of the safety of the use of these products in the clinical trials. The database also facilitates communication on this review and the safety of these clinical trials between the authorities. This process enables each of the Member States to better oversee clinical trials and medicinal product development, and to provide for enhanced protection of clinical trial subjects and patients receiving medicinal products. The database will be the clinical trial module of the Eudravigilance database.

The SUSARs will be entered into a clinical trial module of the Eudravigilance database, thus creating a single overall database for European regulatory authorities covering clinical trial safety reporting and post-marketing safety reporting. Thus, Eudravigilance will consist of one entity containing post-marketing ICSRs (Individual Case Safety Reports) as required by Directive 2001/83/EC and Volume 9 of Eudralex, and clinical trial SUSARs as required by Directive 2001/20/EC.

This document should be read in conjunction with the detailed guidance on the European clinical trials database (Eudract), the Note for Guidance – Regulatory Transmission of ICSRs in Pharmacovigilance (EMEA/H/31387/01/FINAL), and implementing texts of Directive 2001/20/EC provide relevant information, in particular in the ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’.

## **2 Scope**

This detailed guidance document provides the higher level user requirements and system definition necessary for the electronic reporting of SUSARs to the concerned competent authorities, the entry of this information into the database and its distribution to the competent authorities of the Member States, the Agency and the Commission.

The system specification, design, and user documentation will be developed on the basis of this document.

The scope of this guidance includes all clinical trials, as defined by Directive 2001/20/EC for which at least one site falls within the territory of a Member State of the community. In addition it is a requirement that SUSARs occurring in third countries must be reported and entered in the database where they involve products for which there are clinical trials being conducted in the community, by the same or associated sponsors.

This database referred to in article 17.3(a) of Directive 2001/20/EC, is for Suspected Unexpected Serious Adverse Reactions. It is closely linked for the identification of the product and clinical trial, and other clinical trial information, to the Eudract database established under article 11 of the Directive 2001/20/EC. The Eudract database and the Eudravigilance clinical trial module will share common key fields including the clinical trial identification (Eudract number and sponsor protocol code number), the product identification and the sponsor identification. There will be an interface connecting the databases.

This guidance includes or references the standards for reporting these reactions, the data requirements, dictionary coding requirements, the process for reporting including electronic reporting of these reports to the competent authorities and the Agency, the distribution of the reports to all the competent authorities, and the steps taken to ensure confidentiality.

The guidance addresses the procedures for data entry and control, the methods for electronic communication of the data and steps taken to ensure the confidentiality of the data.

### **3 Definitions:**

The definitions of the Directive 2001/20/EC and of the implementing texts adopted in line with that Directive apply. The relevant definitions developed for the Eudravigilance database of post-marketing adverse drug reactions also apply as well as relevant definitions developed in Community guidelines, which have been adopted by the CPMP and published by the Agency. The standards for reporting SUSARs are defined in 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use' and are consistent with ICH E2A, and with the application of ICH-E2BM (CPMP/ICH/287/95 as modified) and ICH-M2-E2BM (CPMP/ICH/285/95 as modified) to clinical trial SUSAR reporting.

Electronic reporting, as defined in this guidance, is the expected and sufficient method for expedited reporting of SUSARs to the competent authorities of the Member States and these reports are to be made in compliance with the timelines set out in the Directive 2001/20/EC and 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'.

### **4 Legal Basis**

The legal basis is set out in Directive 2001/20/EC in articles 11, 17 and 18.

### **5 User Requirements**

The requirements of Directive 2001/20/EC are best met by a database that is accessible to the competent authorities, the Commission, and the Agency and to which the SUSARs and their follow-up are reported directly and electronically by the sponsors concerned.

The competent authorities of the Member States require a European database of SUSARs for purposes including:

- Provision of an overview of SUSAR occurrence in all clinical trials in the community
- Facilitation of communication between competent authorities of the Member States, the Commission and the Agency on SUSARs
- Separate review of SUSARs occurring in a single Member State
- Separate review of clinical trial related and/or post marketing pharmacovigilance reports
- Generation of signals concerning the safety of investigational medicinal products
- Through its interface with the Eudract database, review of safety data in particular populations, groups of products, therapeutic areas etc. including the potential to generate some denominators for safety assessment of products
- Review of SUSARs including those linked with:
  - a given product
  - trials conducted by a given sponsor
  - a patient population type (e.g. age group, gender)
  - a product type
  - a therapeutic category/pathology/indication
  - a type of reaction
  - by frequency (e.g. frequency relative to all reports or a subset of these)
- Generation of statistics on SUSARs
- Through its interface with the Eudract database, ready access to certain reference information relating to each trial for SUSAR review, scientific review, and inspection.

Sponsor requirements: a copy of their reports as they appear in the system, appropriate security and confidentiality of information, continuity, user-friendliness, availability, help information and user documentation.

## **6 Roles and responsibilities**

The clinical trial module of Eudravigilance will be established and maintained by the Agency.

The Member States shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product that are brought to their attention are

immediately entered in the Eudravigilance CT Module. This should be achieved by electronic reporting by the sponsor.

The community sponsor reports all SUSARs electronically. This shall include electronic reporting of 3<sup>rd</sup> country SUSARs.

All SUSARs occurring in the community shall be sent electronically by the sponsor to the Member State in whose territory the reaction occurred, and to the other concerned Member States and the Agency (Eudravigilance CT Module).

Third country reports shall be sent, electronically by the sponsor to the concerned Member States and the Agency (Eudravigilance CT Module).

The responsibilities of the sender, reporter and recipient are set out in the Electronic Data Interchange Agreements - Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance. The Interchange Agreements will be adapted, where applicable, to the requirements of clinical trials.

The Agency makes the database available to receive electronically reported SUSARs.

The Agency makes the information notified by the sponsor available to the competent authorities of the Member States through the establishment and maintenance of the database and making the database available to the competent authorities of the Member States and to the Commission.

The competent authority of each Member State is responsible for the activities involved in assessing the safety of the investigational medicinal products used in the clinical trials occurring on its territory.

The reporting requirements relative to different situations concerning the marketing status in the community, and the source of the report are outlined in Table 1. Whilst the table seeks to address the common scenarios, concerning clinical trials and reporting to Eudravigilance in relation to these, it is not intended to be exhaustive nor to substitute for the applicable legislative requirements and guidelines.

Table 1:  
SUSAR reporting requirements and reporting requirements for serious unexpected ICSRs of non-clinical trial origin, in the context where clinical trials are ongoing in Europe

Case Type	Community Market Status	Origin	Destination	Timeline	Format	Reference
<b>Reports where clinical trials are ongoing in EU</b>						
<b>Originating from clinical trials</b>						
Clinical Trial	Pre	EU <sup>1</sup>	EV CT <sup>2</sup>	7/15 days	E2B <sup>3</sup>	Dir 2001/20/EC
Clinical Trial	Post	EU	EV CT	7/15 days	E2B	Dir 2001/20/EC
Clinical Trial	Pre	exEU <sup>4</sup>	EV CT	7/15 days	E2B	Dir. 2001/20/EC
Clinical Trial	Post	exEU	EV CT	7/15 days	E2B	Dir. 2001/20/EC
<b>Originating from sources other than clinical trials</b>						
Spontaneous report	Pre	EU	EV CT	7/15 days	E2B	Dir. 2001/20/EC
Spontaneous report	Post	EU	EV PM <sup>5</sup>	15 days	E2B	Dir 2001/83/EC, Reg2309/93/EC, Eudralex Vol 9
Spontaneous report	Pre	exEU	EV CT	7/15 days	E2B	Dir. 2001/20/EC
Spontaneous report	Post	ex EU	EV PM	15 days	E2B	Dir 2001/83/EC, Reg2309/93/EC, Eudralex Vol 9

<sup>1</sup> EU = Report of a SUSAR occurring in the community

<sup>2</sup> EV CT = Eudravigilance Clinical Trial Module

<sup>3</sup> E2B = ICH-E2BM and ICH-M2-E2BM

<sup>4</sup> exEU = Report of a SUSAR occurring outside the community

<sup>5</sup> EV PM = Eudravigilance post marketing database

*As both clinical trial SUSARs and post-marketing ICSRs will be held in Eudravigilance it is logical that where a report is made concerning a case to Eudravigilance, it should only be made once and in accordance with the applicable legislation.*

Within each Member State there may be more than one database (e.g. one for clinical trial SUSARs and one for post-marketing ICSRs). Where a Member State requires the reports to be directed to one or other national database the Member State should set up arrangements to direct reports received to the appropriate national database, (using the flags or data fields indicating the origin of the reports (both geographical and in terms of being of clinical trial or non clinical trial origin or other fields that may be appropriate)).

Sponsors do not have access to the Eudravigilance Clinical Trial Module. For reasons of quality control, to permit assurance of consistency by the sponsor and for sponsors to be able to avail of the opportunity to analyse their data, it is desirable to provide them with an up to date copy of their SUSAR reports as they appear in the Eudravigilance database. Provision will therefore be made to provide each sponsor with an export, from the Eudravigilance Clinical Trial module, of the data reported by that sponsor and updates to this, in an electronic form consistent with the data standards applying to the Eudravigilance Clinical Trial module.

## **7 Identification of the clinical trial**

Each SUSAR report shall clearly identify the clinical trial in which it occurred.

The Eudract number will identify each clinical trial, taking place in the community. The sponsor protocol code number will also be entered on SUSAR reports. In the case of studies which are conducted entirely outside the community, and for which no Eudract number is available, the sponsor protocol code number serves as a key study identifier.

Using the Eudract clinical trial number and the identification of the product (see Section 8 below), the system will enable each (valid) report to be linked with the product(s) and clinical trial(s) involving the product(s) that are ongoing or have taken place in the community.

## **8 Identification of the product**

Each investigational medicinal product needs to be uniquely identifiable. The identification of the suspect product(s) shall be ensured by the reports themselves and by the coding processes used in the database.

Each product will be identified in a product dictionary. The dictionary will be that of Eudravigilance, reflecting the requirements for identification of products through their development cycle. This identification will be the same as that provided in the Eudract database which will share the product dictionary.

Where several active substances are combined in one product, each should be individually identifiable.

The product (and substance) needs to be clearly traceable and identifiable throughout its development and use in different clinical trials, and through to post-marketing for those products which are, or become, available on the market in the community.

Where the name of a product or substance changes or is supplemented with an additional name or code, these changes or additions should be linked to previous names or codes.

## **9 Data to be entered into the database**

SUSARs are defined in the ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’. The key data elements are defined in the Community guidelines on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95(ICH E2A)) and on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95 (ICH E2BM)) as modified.

The Eudravigilance data model is based on CPMP/ICH/287/95 (ICH E2BM) as modified.

In accordance with ICH E2BM and CPMP/ICH285/95 (ICH-M2-E2BM) reports may be submitted as XML messages or via web based forms.

The identification of the trial by the Eudract number, sponsor protocol code number, as well as the Eudravigilance and sponsor case number, and study subject code, form part of the data set.

Clinical trial reports are flagged to allow separate analysis of clinical trial reports and post-marketing reports. This will include a process to identify those reports which are both of clinical trial origin and relate to products with marketing authorisations in the community.

Clinical trial reports are flagged to identify the Member State or third country where the reaction occurred, thus allowing analysis of the reactions occurring in individual Member States to be performed separately.

The database will have a process for bringing new reports to the attention of the competent authorities of the Member States, the Agency and the Commission.

The sponsor codes the reports in accordance with the controlled terminologies required for the Eudravigilance database, which include MedDRA and the product dictionary.

## **10 Data entry procedures**

The community sponsor is responsible for ensuring that the reports are sent via the electronic reporting system to the database.

Electronic reports are sent by the sponsor to the concerned Member States and the Agency and the Agency makes them available to the competent authorities of all Member States, the Agency and the Commission, from the time of first entry.

The system will provide the reporter with an acknowledgement of each report, received into the system, in line with the provisions of Eudravigilance.

Reports and follow-up information may be submitted as XML messages or via web based forms, available through the websites of the competent authorities, the Agency and the Commission as well as through dedicated website(s).

Data consistency is enforced through form design and by use of pick lists, dropdown menus and dictionaries or automatically generated codes or text as appropriate and feasible. For this reason use of free text will be restricted to those fields to which it is appropriate.

### 10.1 Registration of sponsors

Each sponsor registers single or multiple users with the system. The reporting task may be delegated to other parties but the sponsor retains ultimate responsibility for SUSAR reporting to the competent authorities.

### 10.2 Identification of reports

- Each report will be identified by the Eudract number and the sponsor protocol code number for the clinical trial involved or where the trial is not being conducted in the community by the sponsor protocol code number.
- Sponsor's case number.
- Suspect product(s).
- Study subject code
- Eudravigilance report number, following first entry of the case in Eudravigilance.

### 10.3 Timing of reporting

The sponsor must complete and submit the reports in compliance with the timelines set out in Directive 2001/20/EC and the 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'.

#### 10.4 Data correction or rejection

The elements constituting the minimum requirements for a report are identified in the 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'. Only reports meeting these minimum requirements will be accepted by the electronic reporting system and the database.

Sponsors are responsible for submitting reports that are complete and accurate based on the information available to them at the time of reporting, and within the constraints of the expedited reporting process. Sponsors are responsible for providing timely, additional follow-up reports and/or corrections and for responding to queries from the competent authorities of the Member States or the Agency.

#### 10.5 Duplicate reports

The database will run checks to determine whether a report received is a duplicate, and flag this for query.

#### 10.6 Follow-up reports

The system will permit the submission of follow-up reports and will link these to the initial reports. The chronology of the reports will be evident.

#### 10.7 Data Quality Assurance and Quality Control

It is the responsibility of the party making the data submission, coding or entry to ensure the accuracy and completeness of the data at the time it is first entered.

Staff (at the sponsor and at the competent authority, the Agency or the Commission) responsible for data submission/validation/entry/review should be trained for the purpose and have standard operating procedures available to them. Quality control and assurance systems should be in place to verify the accuracy and integrity of the data entry.

The database will include automated checks to ensure internal consistency, to check that valid terms are used and to validate where possible, information included. These functions will be capable of generating reports for the purposes of quality review and management of the database.

The database system will be equipped with an electronic audit trail to identify the date, time and source of original entries and any changes to these, including the identity of the party making the original and any new or changed entry. The audit trail will function in such a way as to ensure the old entries as well as the most recent version can be viewed. Where appropriate the reason for change will be recorded (standard reasons will be provided by drop down menu).

## 10.8 Language

In order to facilitate the implementation of the database, and to enable search and reporting functions, data should be entered in English. Where feasible dropdown menus/pick lists may be provided in the official languages. It is recognised that not all dictionaries will be available in all official languages and may initially exist only in English. Translations of dictionaries will only be used where the originators of the dictionaries make full and current versions available. Whenever required by a Member State the sponsor will submit the narrative in the official language of the Member State, in whose territory the reaction has occurred, this narrative should also be entered in English.

## 10.9 Backup

The European Database Manager will ensure appropriate, regular backup, on electronic media, of the system and data contents, to permit restoration in case of loss or damage to the database and reporting mechanisms.

The availability of the reporting interface on the websites of the competent authorities of the Member States, the Agency and the Commission will provide additional safeguards on the continued availability of the system.

## **11 Links with other databases**

There will be an interface between this database and the Eudract database.

The database will be compatible with other community regulatory authority databases, in particular Eudract, as far as data structure and electronic transmission and exchange standards are concerned.

It is the responsibility of Member States to enable download/upload of data to/from their national databases and this, Eudravigilance - Clinical Trial Module database, where the Member State(s) consider this appropriate. The Eudravigilance Clinical Trial Module data will be in a format that facilitates such operations, however a single data structure will be used for each item.

## **12 Data confidentiality**

The security standards that apply will, as a minimum, be those set by the European Commission for the operation of secure networks for regulatory authority communication, and consistent with those developed for Eudravigilance. Access to the database is restricted to the competent authorities of the Member States, the Agency and the Commission.

The database of SUSARS will contain data relating to specific study subjects/patients. The patient's right to confidentiality is paramount. The patient's identity in the

SUSAR report forms, that enter the database, should be codified. Identifiable personal details must always be kept in confidence. Personal data should be protected in accordance with the provisions of GCP and Directive 95/46/EC (as required by Directive 2001/20/EC) and in keeping with community pharmacovigilance requirements (Volume 9 of the rules governing medicinal products in the European Union).

Member States must respect the confidentiality of information downloaded from the database to national databases in line with Directive 2001/20/EC and this detailed guidance.

### **13 Electronic data communication between competent authorities of the Member States, the Agency and the Commission**

Electronic communication will be enabled using the current community secure network for regulatory authority communication.

The standards are those of ICH E2BM, ICH M2-E2BM and those developed for Eudravigilance

For details on electronic data communication of safety reports reference should also be made to the relevant sections of Volume 9 of the Rules governing medicinal products in the European Union (EU electronic exchange of pharmacovigilance information) and associated guidelines including Community guidelines and those for the post-marketing Eudravigilance systems.

### **14 Reporting and Search Functions**

The database will be provided with a number of pre-established search and report functions.

The database will be provided with a number of search functions that will permit the location of specific information using key data items and generation of a range of ad hoc reports based on this function and the relations between the data items. These will include links with the Eudract database.

The database will provide a number of management reports to facilitate its use, quality control and maintenance.