



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
ENTR/CT 3

Revision 1

**Detailed guidance on the collection, verification
and presentation of adverse reaction reports arising
from clinical trials on medicinal products for
human use**

April 2004

Table of contents

	Page
1. Introduction	3
2. Legal Basis	3
3. Scope	3
4. Definitions	3
5. Investigator's Responsibilities	3
6. Sponsor's Responsibilities	4
6.1 General Remarks	4
6.2 Recording and Evaluation of Adverse Events (AEs)	4
6.2.1 Assessment of seriousness	4
6.2.2 Assessment of causality	4
6.2.3 Sponsor's assessment of expectedness	5
6.2.4 Data protection of trial subjects	5
6.3 Reporting of Serious Adverse Reactions (SARs)	5
6.3.1 Standards for expedited reporting	5
6.3.1.1 What must be reported?	5
6.3.1.1.1 Suspected unexpected serious adverse reactions (SUSARs)	5
6.3.1.1.2 Other safety issues requiring expedited reporting	5
6.3.1.2 What should not be reported?	6
6.3.1.3 Who should report and whom to report to?	6
6.3.1.4 Managing SUSARs associated with active comparator or placebo	6
6.3.1.5 When to report ?	6
6.3.1.5.1 Fatal and life-threatening SUSARs	6
6.3.1.5.2 Non fatal and non life-threatening SUSARs	6
6.3.1.6 How to report?	7
6.3.1.6.1 Minimum criteria for initial expedited reporting of SUSARs	7
6.3.1.6.2 Follow up reports of SUSARs	7
6.3.1.6.3 Format of SUSARs reports	7
6.3.1.6.4 Form and format of the reports about other observation also qualifying for expedited reporting	7
6.3.1.6.5 How to inform the Ethics Committee	8
6.3.1.7 SUSARs identification and management of follow up and duplicate reports	8
6.3.1.8 Managing adverse reactions/events in blinded trials	8

6.3.1.9	Managing adverse reactions/events in trials with high morbidity and high mortality diseases and where efficacy end-points could also be SUSARs	9
6.3.2	Annual safety reports	9
6.3.2.1	Content of the annual safety report of a clinical trial	9
	Report on subjects safety of a clinical trial	9
	Line listings	10
	Aggregate summary tabulations	10
6.3.2.2	Reporting time frame for annual safety report	11
6.4	How to inform the investigators?	11
6.5	Reporting of safety issues following completion of the clinical trial in European Community	12
Annex 1:	Comments on definitions and abbreviations	13
Annex 2:	Member States' contact points for reporting	15
Annex 3:	Data elements for SUSAR report	19
Annex 4:	Content of line listing	21
Annex 5:	Example for an aggregate summary tabulation	22

1. Introduction

This document sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

2. Legal Basis

Article 18 of Directive 2001/20/EC requires the Commission to publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions. The present guidance fulfils the obligations laid down in this Article.

3. Scope

This guidance applies to all clinical trials on medicinal products for human use conducted within the European Community. It applies to all investigational medicinal products (IMPs) for human use, independently from their marketing authorisation status in any Member State whether or not IMPs are used under the conditions of the marketing authorisation.

It provides detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from such trials. In addition, it sets out the responsibilities of the concerned parties.

4. Definitions

The definitions of Directive 2001/20/EC, Article 2, are applicable. These are further supplemented by terms from the following Community Guidelines where they are related to collection, verification decoding and presentation of adverse reaction reports arising from clinical trials:

Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95),

Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95 modification)

5. Investigator's Responsibilities

The responsibilities of the investigator in relation to the notification of Adverse Events (AEs) are set out in Directive 2001/20/EC: “ The investigator shall report all Serious Adverse Events (SAEs) immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The initial report shall be promptly followed by detailed, written reports. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter”.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to the sponsor by the investigator according to the reporting requirements within the time periods specified in the protocol.

The investigator shall supply the sponsor and the Ethics Committee with any additional requested information, notably for reported deaths of a subject.

6. Sponsor's Responsibilities

6.1 General Remarks

The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s).

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Ethics Committee and competent authority of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The sponsor is responsible for arranging structures and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

6.2 Recording and Evaluation of Adverse Events (AEs)

Individual adverse events should be evaluated by the investigator and where indicated by the guidance in section 5, they should be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor has to keep detailed records of all AEs reported to him by the investigator(s) and to perform an evaluation with respect to seriousness, causality and expectedness.

On request of a competent authority in whose territory the clinical trial is being conducted, the sponsor should submit detailed records of all adverse events which are reported to him by the relevant investigator(s).

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

6.2.1 Assessment of seriousness

Seriousness shall be determined according to the definition in Article 2 of the Directive 2001/20/EC taking into account the comments presented in Annex 1.

6.2.2 Assessment of causality

Causality shall be determined according to the definition of an adverse reaction as given in Article 2 of the Directive 2001/20/EC taking into account the comments presented in Annex 1.

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided with the report.

6.2.3 Sponsor's assessment of expectedness

The definition of the term “unexpected adverse reaction” is given in the Directive 2001/20/EC taking into account comments in Annex 1. Reports have to be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined by the sponsor according to the reference document as defined in the study protocol (e.g. investigator's brochure for an unapproved investigational medicinal product or summary of product characteristics (SmPC) for an authorised medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorisation). When the IMP has a MA in several MS with different SmPCs, the sponsor should select one of them as a reference document for assessing expectedness and must mention it in the protocol.

6.2.4 Data protection of trial subjects

The Community standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

6.3 Reporting of Serious Adverse Reactions (SARs)

6.3.1 Standards for expedited reporting

6.3.1.1 What must be reported ?

6.3.1.1.1 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an IMP (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Additionally for IMPs that have not a marketing authorisation in any MS of the European Community, any other SUSAR associated with the IMP and as soon as the sponsor becomes aware of them are subject to expedited reporting. This includes:

- SUSARs which occur in another trial conducted by the same sponsor either in European Community or in a third country (i.e. in non European Community countries),
- or which are identified by spontaneous reports or a publication,
- or which are transmitted to the sponsor by another regulatory authority.

6.3.1.1.2 Other safety issues requiring expedited reporting

Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reactions with an unexpected outcome (e.g. : a fatal outcome),
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,

- new event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as :
 - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
 - a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
 - a major safety finding from a newly completed animal study (such as carcinogenicity).
 Where the IMP is authorised in a MS and the sponsor is the marketing authorisation holder, the reporting of SUSARs should take into account national requirements intended to manage duplication of reports in the context of the Directive 2001/83/EC, Regulation 2309/93/EC and the: ‘Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)’.

6.3.1.2 What should not be reported ?

Expedited reporting is not usually required:

- for reactions which are serious but expected,
- for non-serious adverse reactions whether expected or not.

It is usually also inappropriate to report events that are considered unrelated to the investigational medicinal product.

6.3.1.3 Who should report and whom to report to?

The sponsor should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned (see section 6.3.1.6.5).

The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects (see section 6.4).

6.3.1.4 Managing SUSARs associated with active comparator or placebo

The sponsor must report to the competent authority and the Ethics Committee of the concerned Member States all SUSARs associated with a comparator product in the concerned clinical trial even if this product is authorised. In addition, it is recommended that the sponsor report them to the marketing authorisation holder and inform it of the previous notification to the competent authority. But in all cases reporting SUSARs from a clinical trial to the competent authority should only take place through the sponsor.

Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient), it is the sponsor's responsibility to report such cases.

6.3.1.5 When to report ?

6.3.1.5.1 Fatal or life-threatening SUSARs

The competent authority and the Ethics Committee in the concerned Member States should be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the Ethics Committee in the concerned Member States within an additional eight calendar days.

6.3.1.5.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues, described in section 6.3.1.1.2, must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

6.3.1.6 **How to report ?**

6.3.1.6.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

- a) a suspected investigational medicinal product,
- b) an identifiable subject (e.g. study subject code number),
- c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- d) an identifiable reporting source,

and, when available and applicable:

- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

6.3.1.6.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

6.3.1.6.3 Format of the SUSARs reports

Electronic reporting should be the expected method for expedited reporting of SUSARs to the competent authority. In that case, the format and content as defined by the Guidance¹ should be adhered to.

The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances; for initial expedited reporting see also section 6.3.1.6.1).

The latest version of MedDRA should be applied, using version 4.1 or later versions. Lower level terms (LLT) should be used.

6.3.1.6.4 Form and format of the reports about other important safety issues also qualifying for expedited reporting

Other important safety issues also qualifying for expedited reporting (see section 6.3.1.1.2), should be notified by a letter under the heading of safety report. The first page of the report

¹ *Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance-Clinical Trial Module)*

should reference the EudraCT number, the title and the sponsor's trial protocol code number of the trial to which it refers and points of concern summarised in a short section.

6.3.1.6.5 How to inform the Ethics Committee ?

In accordance with national legislation, the Ethics Committee concerned may only receive expedited individual reports of SUSAR that occurred in subjects who have been recruited at that Member State, provided that:

- a) All SUSARs from Member States and, where applicable, from third countries are reported at least quarterly, as a line listing accompanied by a brief report by the sponsor highlighting the main points for concern. In that case, a copy should be sent to the competent authority concerned.
- b) Any changes increasing the risk to subjects and any new issues that may affect adversely the safety of the subjects or the conduct of the trial should also be provided as soon as possible, but not later than fifteen days.

6.3.1.7 SUSARs identification and management of follow-up and duplicate reports

Each initial and follow-up SUSAR report should contain enough information to allow identification of duplicate reports. Particularly, the identification code of the patient who experienced a SUSAR must be unique in the same clinical trial whatever the number of SUSARs and the time at which they occurred.

If duplicates are identified by the sponsor, the concerned competent authority and the Ethics Committee concerned shall be informed accordingly.

In accordance with national legislation, sponsors may be able to fulfil their obligation to reports SUSARs to the MS competent authority by reporting them directly to the EMEA database established under Article 11(1) of the Directive 2001/20/EC. This will avoid duplicate reporting to the EMEA database where the same trial is conducted at sites in more than one Member State and would result in more than one MS making the same report to the EMEA database.

6.3.1.8 Managing adverse reactions/events in blinded trials

As a general rule treatment codes should be broken by the sponsor before reporting a SUSAR to the competent authority and the Ethics Committee of the concerned Member States.

Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse event may be a serious adverse reaction unexpected or otherwise is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for data-analysis and interpretation of results at the study's conclusion. The unblinding of single cases by investigators in the course of a clinical trial should only be performed if relevant for the safety of the trial subject.

It is recommended that in case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship as if it was the tested IMP that caused the reaction. If the case appears to be a SUSAR then it should be unblinded. Then two possibilities have to be taken into account.

- a) If the administered product is the tested IMP, the case would be reported as a SUSAR to the relevant Competent Authorities and the relevant Ethics Committees.
- b) If the administered product is a comparator with a marketing authorisation, the adverse reaction should be reassessed for expectedness according to the SmPC as included in the study protocol. If the adverse reaction is unexpected then the SUSAR should be reported; otherwise it is an expected serious adverse reaction and not reportable on an expedited basis.

6.3.1.9 Managing adverse reactions/events in trials with high morbidity and high mortality diseases and where efficacy end-points could also be SUSARs

For trials in high morbidity and/or high mortality disease, where efficacy end-points could also be SUSARs or when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with competent authorities in advance concerning serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting. Modalities for reporting these adverse reactions must be clearly defined in the protocol.

For those trials, sponsors are strongly encouraged to appoint an independent Data Monitoring Committee (DMC) in order to review on a regular basis and when necessary safety data on the ongoing trial and to recommend to the sponsor whether to continue, modify or terminate the trial. This procedure must be described in the protocol. The DMC opinion and recommendations should be notified as soon as possible by the sponsor to the competent authority and the Ethics Committee in the concerned Member State where they qualify for expedited reporting (see section 6.3.1). However cases of SUSARs, in these same studies, that are not efficacy endpoints should be reported as usual.

6.3.2 Annual safety reports

In addition to the expedited reporting, sponsors shall submit, once a year throughout the clinical trial or on request a safety report to the competent authority and the Ethics Committee of the concerned Member States, taking into account all new available safety information received during the reporting period. This global analysis should be the same for the competent authorities concerned and the Ethics Committee concerned.

6.3.2.1 Content of the annual safety report of a clinical trial

The annual safety report of a clinical trial should have three parts:

- a report on the subjects' safety in the concerned clinical trial
- a line listing of all suspected SARs (including all SUSARs) occurred in the concerned trial,
- an aggregate summary tabulation of suspected SARs that occurred in the concerned trial.

Report on the subjects' safety of a clinical trial

The sponsor has to provide a concise safety analysis and benefit-risk evaluation for the clinical trial concerned. It should describe in a concise way, all new findings known by the sponsor related to the safety of the IMP treatments in the concerned trial and provide critical analysis of them with respect to their impact for the subjects of the concerned trial. The concept of new findings refers to information not already present in the investigator's brochure or SmPC.

It should be complemented with an analysis of the implications for the population of the clinical trial and should also analyse the safety profile of the tested IMP and its implication to sub-

jects' exposure, taking into account all available safety data. When relevant, the following points should be considered:

- a) relation with dose, duration, time course of the treatment
- b) reversibility
- c) evidence of previously unidentified toxicity in the trial subjects
- d) increased frequency of toxicity
- e) overdose and its treatment
- f) interactions or other associated risks factors
- g) any specific safety issues related to special populations, such as the elderly, the children or any other at risk groups.
- h) positive and negative experiences during pregnancy or lactation
- i) abuse
- j) risks which might be associated with the investigation or diagnostic procedures of the clinical trial

The report should also consider supporting results of non-clinical studies or other experience with the investigational medicinal product that are likely to affect the subjects' safety. It should detail the measures previously or currently proposed to minimise the risks found where appropriate. Finally, a detailed rationale must be given on whether or not it is necessary to amend the protocol, to change or update the consent form, patient information leaflet and the investigator's brochure. This report will not replace the request for protocol amendments, which will follow its own specific procedure.

Line-listings

The annual report should contain a trial-specific line-listing of all reports of suspected SARs that were reported during this trial.

The line listing provides key information but not necessarily all the details usually collected on individual cases.

It should include each subject only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis) as judged by the sponsor.

It is possible that the same subject may experience different adverse reactions on different occasions. Such experiences should be treated as separate reports. Under such circumstances, the same subject might then be included in a line listing more than once and the line-listings should be cross-referenced when possible.

Cases should be tabulated by body system (standard system organ classification scheme).

The line listing identifiable by the sponsor listing reference number or date and time of printing should include the information per case as described in annex 4.

Usually there should be one listing for each trial, but separate listings might be provided for active comparator or placebo or when appropriate and relevant for other reasons, e.g. in the case that in the same trial for different formulations, indications or routes of administration are studied.

Aggregate summary tabulations

In addition to individual cases line listings, summary tabulations of SAR terms for signs, symptoms and/or diagnoses across all patients should usually be presented to provide an overview for the trial. These tabulations ordinarily contain more terms than subjects.

When the number of cases is very small, a narrative description would be more suitable.

The aggregate summary tabulation should specify the number of reports :

- a) for each body system
- b) for each ADR term
- c) for each treatment arm, if applicable (IMP, comparator or placebo, blinded treatment).

The unexpected ADR terms should be clearly identified in the tabulation. As an example, the table in annex 5 can be used.

When the sponsor conducts several clinical trials with the same tested IMP, a single annual safety report referring to several trials could be acceptable. In that case :

- a concise global analysis on the safety profile of the tested IMP taking into account all new findings related to the safety of the tested IMP in the concerned clinical trials and an analysis of the implications of the findings for the population included in each clinical trial covered by the report,
- and the annual safety report relating to each clinical trial concerned.

6.3.2.2 Reporting time frame for annual safety report

The reporting time frame for annual reports starts with the date of the first authorisation of the concerned clinical trial by a competent authority in any Member State.

This date is designated as the cut off for data to be included in the annual safety report. The sponsor should submit annual reports within 60 days of the data lock point.

However, if a sponsor conducts several clinical trials with the same tested investigational medicinal product in any Member State, he should prepare only one safety report covering the information necessary for all those trials, the reporting period starts with the date of the authorisation for the first of these trials by the competent authority in any Member State and ends after close of the last trial in any MS. If the sponsor is the marketing authorisation holder (MAH) of the tested IMP, the reporting period should be aligned with the International Birth Date. However, Annual Safety Report and Periodic Safety Update Report (PSUR) must be stand-alone documents.

If the IMP is granted a marketing authorisation for the first time in any MS while it is being tested in a clinical trial, the reporting time frame for the IMP would change from the first date of authorisation of a clinical trial in a MS to the international birth date.

In the case of short term trials (less than 6 months), the safety report may be notified within 90 days of the end of trial together with the notification of the end of the trial according to Directive 2001/20/EC article 10 c). This report should contain at least line listings, if appropriate aggregate summary tabulations and a statement of the patients safety.

6.4 How to inform the investigators?

The sponsor shall inform all investigators concerned on findings that could adversely affect the safety of study subjects. If appropriate, the information can be aggregated in a line listing of SUSARs in periods as warranted by the nature of the clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product.

In the case of blinded trials the line listing should present data on all SUSARs, regardless of the medication administered (e.g. active/placebo), thereby when possible and appropriate, the blind would be maintained and the risk of inadvertently informing the investigators with regard to the identity of the medication would be avoided.

If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, the sponsor should issue as soon as possible a communication to all investigators.

A safety issue that impacts upon the course of the clinical study or development project, including suspension of the study programme or safety-related amendments to study protocols should also be reported to the investigators.

6.5 Reporting of safety issues following completion of the clinical trial in European Community

After termination of the clinical trial , any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the competent authority(ies) concerned together with proposed actions.

Annex 1: Comments on definitions and abbreviations

- **Adverse event (AE):** *any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.*

Comment: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

- **Adverse reaction of an investigational medicinal product (AR):** *all untoward and unintended responses to an investigational medicinal product related to any dose administered.*

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

- **Unexpected adverse reaction:** *an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).*

Comments:

- When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

- **Severity:** The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

- **Serious adverse event or serious adverse reaction:** *any untoward medical occurrence or effect that at any dose*
 - *results in death,*
 - *is life-threatening*
 - *requires hospitalisation or prolongation of existing inpatients' hospitalisation,*
 - *results in persistent or significant disability or incapacity,*
 - *is a congenital anomaly or birth defect.*

Comments:

- Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Medical judgement should be exercised in deciding whether an adverse event/ reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

- **Concerned Member State:** Member State in whose territory a clinical trial with the investigational product is being performed.
- **Ethics Committee Concerned:** Ethics Committee that gave the favourable opinion for a clinical trial on the investigational product in a Member State according to Art. 7 of the Directive 2001/20/EC.
- **Investigators Concerned:** *Investigators, which are* actively involved in running clinical trials on the tested investigational medicinal product
- **Data Lock-Point (cut-off date)²:** *The date designated as the cut off date for data to be included in a annual safety report*
- **International Birth Date (IBD)³:** The date of the first marketing authorisation for a medicinal product granted to the marketing authorisation holder (MAH) in any country in the world.²
- **Periodic Safety Update Report (PSUR)⁴ for a medicinal product with a marketing authorisation:** All records of adverse reactions shall be submitted to the competent authorities in form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and at the time of the first renewal. Thereafter the periodic safety update report shall be submitted at five-yearly intervals together with the application for renewal of the authorisation. The periodic safety update report shall include a scientific evaluation of the benefit and risks afforded by the medicinal products.

² Volume 9 – Pharmacovigilance Medicinal Products for Human and Veterinary use, page 142

³ page 143

⁴ Directive 2001/83/EC Article 1 No. 14 and Article 104 No. 6

Annex 2: Member States' Contact points for Reporting (will be up-dated in due course)

The Member States' contact points for reports of adverse reactions occurring in clinical trials on human medicinal products are as follows:

Member state	Contact point
Belgium	Federal Public Service Health, Food Chain Safety and Environment Directorate-General Medicinal Products Unit IX – Clinical trials Bischhoffsheim 33, 1 st floor 1000 Brussels, Belgium Phone: + 32 (0) 2 227 55 77 Fax: + 32 (0) 2 227 55 31
Denmark	The Danish Medicines Agency Clinical Trials, Inspection and Enforcement Division Axel Heides Gade 1 DK-2300 Copenhagen S Phone: + 45 44 88 95 95 Fax: + 45 44 88 93 14 www.dkma.dk
Finland	
France	Agence Francaise de Sécurité Sanitaire des Produits de Santé (AFSSAPS) DEMEB/Unité Essais Cliniques 143/147, Boulevard Anatole France 93285 Saint-Denis Cedex Phone: +33-1-55-87-36-43 Fax: +33-1-55-87-36-42
Germany	Federal Institute for Drugs and Medicinal Devices Kurt-Georg-Kiesinger-Allee 3 D-53175 Bonn Phone +49-228-207/4320 Fax: +49-228-207 home page Paul-Ehrlich-Institut Paul-Ehrlich-Str. 51-59 D-63225 Langen Phone: +49 6103-77-1010/1011 Fax: +49 6103-77-1263 Home page: www.pei.de e-mail: kelbr@pei.de

Greece	National Organization for Medicines (EOF) Division of Pharmaceutical Studies and Research 284 Mesogeion Avenue 15562 Athens Greece Tel + 30 210 6507200 Fax + 30 210 6549585 Home page www.eof.gr e-mail adr & eof-gr
Italy	Ministry of Health General Directorate for Drug and Medicinal Viale Civiltà Romana, 7 00 144 ROMA Phone : +39-06 5994 3483 Fax : + 39-06 5994 3227
Ireland	Drug Safety Associate, Pharmacovigilance Unit, Irish Medicines Board; Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland Phone: + 353-1-676 4971 Fax: + 353-1-676 2517 Home page: www.imb.ie
Luxembourg	Direction de la Santé Division de la phammacie et des Médicaments Villa Lowigny Allée Marconi L-2120 Luxembourg Tel: +352 478 55 93/55 90 Fax: +352 26 20 01 40/47
Netherlands	College ter Beoordeling van Geneesmiddelen/Medicines Evaluation Board PO Box 16229 2500 BE Den Haag Phone: +31 70 3406700 Fax. +31 70 3406737
Portugal	INFARMED, Departamento de Farnacovigilancia, Sector de Reaccoes Adversas a Medicamentos Parque da Saude de Lisboa

	<p>Av. Do Brasil, 53 1749-004 Lisboa, Portugal Phone: +351 21 7987 100/7142 Fax: + 351 21 7987 100 Home page: www.infarmed.pt</p>
Spain	<p>Agencia Espanola de Medicamentos y Productos Sanitarios Division de Farmacologia y Evaluacion Clinica C/ Alcalá, 5628071 Madrid Fax: +34 91 822 5161</p> <p>When the investigational medicinal product is marketed in Spain , and used under the terms of market authorisation: Division de Farmacoepidemiologia y Farmacovigilancia Paseo del Prado 18-20 28014 Madrid Fax. +34 91 596 78 91</p>
Sweden	<p>Pharmacovigilance Unit Medicinal Products Agency P.O. Box 26 S-751 03 Uppsala Sweden Phone: +46 18 17 56 00 Fax: +46 18 54 85 666 e-mail: registrator@mpa.se home page: www.mpa.se</p>
United Kingdom	<p>MHRA Clinical Trials Unit Market Towers, 12th Floor 1 Nine Elms Lane London SW8 5 NQ Phone: +44 (0) 207 084 2327 FAX: +44 (0) 207 084 2443 e-mail: salma.syed@mhra.gsi.gov.uk</p>
New Member States	
Cyprus	<p>The Registrar Drugs Council PHARMACEUTICAL SERVICES, MINISTRY OF HEALTH</p> <p>1475 LEFKOSIA, CYPRUS</p> <p>Tel.: +357-22-407-132 Fax: +357-22-407-149</p>
Czech Republic	<p>State Institute for Drug Control – Branch of Clinical Trials and Pharmacovigilance Šrobárova 48 100 41 Praha 10</p>

	<p>Fax: +420 272 185 816 Phone: +420 272 185 817 klin.sekret@sukl.cz;</p>
Estonia	<p>Katrin Kiisk State Agency of Medicines 19 Ravila Street 50411 Tartu Estonia Fax: + 372 737 4142 e-mail: katrin.kiisk@sam.ee</p>
Hungary	
Latvia	<p>Janis Ozolins, Head of the Board of State Agency of Medicines, 15 Jersikas street, Riga, LV 1003 Phone: 371-7078400 Fax: 371-7078428 e-mail address: info@vza.gov.lv</p>
Lithuania	
Malta	
Poland	
Slovakia	
Slovenia	
EFTA	
Norway	<p>Norwegian Medicines Agency Section for clinical trials Sven Oftedalsvei 6 NO-0950 OSLO NORWAY Telephone: (+47) 22 89 77 00 Telefax: (+47) 22 89 77 99 Internet: www.noma.no E-mail: klut@noma.no</p>

Annex 3 Data Elements for SUSAR report

1. Clinical trial identification¹:

- Clinical trial identification (EudraCT number, if applicable or the sponsor's trial protocol number),

2. Subject's details :

- Sponsor's subject identification number⁵,
- Initials, if applicable,
- Gender,
- Age and/or date of birth,
- Weight,
- Height,

3. Suspected investigational medicinal product(s) :

- Name of the IMP or brand name as reported,
- International non-proprietary name (INN),
- Batch number,
- Indication(s) for which suspect investigational medicinal product was prescribed or tested,
- Dosage form and strength,
- Daily dose and regimen (specify units e.g. mg, ml, mg/kg),
- Route of administration,
- Starting date and time of day,
- Stopping date and time, or duration of treatment
- Unblinding : yes/no/not applicable ; results¹:
 - * Investigator's causality assessment
 - * Sponsor's causality assessment
 - * Comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s).

4. Other treatment(s) :

- For concomitant medicinal products (including non prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as listed above for the suspected investigational medicinal product.

5. Details of suspected Adverse Drug Reaction (s) :

- Full description of reaction (s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible attempts should be made to establish a specific diagnosis for the reaction.
- Reaction(s) in MedDRA terminology¹ (lowest level term)⁶
- Start date (and time) of onset of the reaction,
- Stop date (and time) or duration of the reaction,
- De-challenge and re-challenge information,
- Setting (e.g. hospital, out-patient clinic, home, nursing home),

⁵ Data not listed in CPMP/ICH/377/95

⁶ EMEA recommendations and ICH E2B (M).B2i 1

- Outcome : information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results ; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available.
- Other information : anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse ; family history ; findings from special investigations.

6. Details on reporter of event/suspected ADR :

- name,
- address,
- telephone number,
- profession (speciality)

7. Administrative and Sponsor details:

- Date of this report
- Source of report: from a clinical trial (provide details if not in Eudract¹, from the literature (provide copy), spontaneous, other,
- Date event report was first received by sponsor,
- Country in which reaction occurred,
- Type of report filed to authorities : initial or follow-up (first, second, etc),
- Name and address of sponsor/manufacturer/company,
- Name, address, telephone number and fax number of contact person in reporting sponsor,
- identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND number, NDA number)
- Case reference number (sponsor's/manufacturer's identification number for the case) (this number must be the same for the initial and follow-up reports on the same case).

Annexe 4 Content of line listing

The line listing identifiable by the sponsor listing reference number or date and time of printing should include the following information per case

- a) clinical trial identification,
- b) Study subjects identification number in the trial
- c) case reference number (Case-ID-Number) in the sponsor's safety database for medicinal products
- d) country in which case occurred
- e) age and sex of trial subject
- f) daily dose of investigational medicinal product, (and, when relevant, dosage form and route of administration)
- g) date of onset of the adverse reaction.
If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible.
- h) dates of treatment. (if not available, best estimate of treatment duration.)
- i) adverse reaction : description of reaction as reported, and when necessary as interpreted by the sponsor ; where medically appropriate, signs and symptoms can be lumped into diagnoses. MedDRA should be used.
- j) patient's outcome (e.g. resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions
- k) comments, if relevant
(e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge / rechallenge results if available)
- l) unblinding results in the case of unblinded SUSARs
expectedness at the time of the occurrence of the suspected SARs, assessed with the reference document (i.e. investigator's brochure) in force at the beginning of the period covered by the report.

Annex 5 Example for an Aggregate Summary Tabulation

Number of reports by terms (signs, symptoms and diagnoses) for the trial n° :
 (An * indicates an example of a SUSAR)

<i>Body system / ADR term</i>	<i>Verum</i>	<i>Placebo</i>	<i>Blinded</i>
<i>CNS</i>			
<i>Hallucinations*</i>	<i>2</i>	<i>2</i>	<i>0</i>
<i>Confusion*</i>	<i>1</i>	<i>1</i>	<i>0</i>
-----	-----	-----	-----
<i>Sub-total</i>	<i>3</i>	<i>3</i>	<i>0</i>
<i>CV</i>			
...			

<i>Sub-total</i>			