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*(Information)*INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES
AND AGENCIES

EUROPEAN COMMISSION

Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')

(2011/C 172/01)

1. INTRODUCTION**1.1. Legal basis**

1. This detailed guidance is based on Article 18 of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use⁽¹⁾ (hereinafter 'Directive 2001/20/EC'), which provides that:

'The Commission, in consultation with the Agency, Member States and interested parties, shall draw up and publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.'

2. According to Article 3(1) of Directive 2001/20/EC, all national provisions on the protection of clinical trial subjects have to be consistent with the procedures and time-scales set out in Directive 2001/20/EC, including procedures and time-scales for the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. This document provides guidance on these aspects.
3. National competent authorities and Ethics Committees of the Member States of the European Union ('EU') and of the Contracting States of the European Economic

Area ('EEA')⁽²⁾, sponsors and investigators, as well as persons to whom tasks and functions related to safety reporting have been delegated, should consider this guidance when applying Directive 2001/20/EC.

1.2. Scope

4. This detailed guidance addresses the collection, verification and reporting of adverse events and adverse reactions which occur in a clinical trial falling within the scope of Directive 2001/20/EC, i.e. a clinical trial as defined therein and performed in at least one EU Member State.
5. For more details on the scope of Directive 2001/20/EC reference is made to section 1.2 of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial⁽³⁾ (hereinafter 'detailed guidance CT-1').

1.3. Definitions

6. The definitions contained in Directive 2001/20/EC, its implementing Commission acts and relevant Commission guidance documents in their current versions also apply in respect of this detailed guidance.
7. Regarding the terms 'adverse event', 'adverse reaction', 'suspected', 'unexpected', and 'serious', reference is made to the respective sections of this detailed guidance.

⁽¹⁾ OJ L 121, 1.5.2001, p. 34.

⁽²⁾ For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA Contracting States, unless indicated otherwise.

⁽³⁾ OJ C 82, 30.3.2010, p. 1.

8. For the purposes of this detailed guidance, 'Member State concerned' means the Member State in which the clinical trial has been authorised by the national competent authority and received a favourable opinion of the Ethics Committee.

1.4. Interface with other guidance documents

9. This detailed guidance is to be read in conjunction with, in particular:

- the detailed guidance CT-1, and
- the Note for guidance on clinical safety data management: Definition and standards for expedited reporting⁽⁴⁾ (hereinafter 'note for guidance ICH E2A').

10. Where appropriate, this detailed guidance reproduces the content of the above-mentioned guidance documents in order to facilitate application of the rules on safety reporting.

2. INTERFACE WITH PHARMACOVIGILANCE RULES

11. The pharmacovigilance rules laid down in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use⁽⁵⁾ (hereinafter 'Directive 2001/83/EC') and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (hereinafter 'Regulation (EC) No 726/2004')⁽⁶⁾ do not apply to investigational medicinal products ('IMPs') and non-investigational medicinal products⁽⁷⁾ ('non-IMPs')⁽⁸⁾.

12. It follows that:

- safety reporting falls *either* under Directive 2001/20/EC or under the provisions on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004. Adverse reactions may not be reported under both regimes, i.e. Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC,

- an adverse reaction to an IMP or non-IMP occurring in a clinical trial is only to be reported or followed up in accordance with Directive 2001/20/EC. In applying that Directive, this detailed guidance should be complied with.

13. Thus, the responsibilities of sponsors and investigators as regards safety reporting are determined only by Directive 2001/20/EC.

3. RESPONSIBILITIES OF THE INVESTIGATOR AND SPONSOR AS REGARDS MONITORING AND SAFETY REPORTING

14. The investigator's responsibilities entail:

- reporting of serious adverse events to the sponsor (see section 4),
- reporting of certain non-serious adverse events and/or laboratory abnormalities to the sponsor (see section 5).

15. The sponsor's responsibilities entail:

- recording of adverse events (see section 6),
- reporting of suspected unexpected serious adverse reactions ('SUSARs') to the national competent authority (be it directly or through the Eudragilance Clinical Trials Module, see section 7.4) and the Ethics Committee (see section 80),
- informing the investigators (see section 7.10),
- annual safety reporting to the national competent authority and the Ethics Committee (see section 8).

16. The sponsor should continuously weigh anticipated benefits and risks of the clinical trial⁽⁹⁾, which includes ongoing safety evaluation of IMPs.

17. The sponsor should arrange for systems and written standard operating procedures to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and following-up.

⁽⁴⁾ CPMP/ICH/377/95 (<http://www.ema.europa.eu/pdfs/human/ich/037795en.pdf>).

⁽⁵⁾ OJ L 311, 28.11.2001, p. 67.

⁽⁶⁾ OJ L 136, 30.4.2004, p. 1.

⁽⁷⁾ For guidance on these terms, see *Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs)* (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm).

⁽⁸⁾ Article 3(3) of Directive 2001/83/EC. See also Article 107(1), 3rd subparagraph of Directive 2001/83/EC, as amended by Directive 2010/84/EU of 15 December 2010.

⁽⁹⁾ Section 2.2. of ICH E6 — Good clinical practice.

18. Regarding clinical trials with advanced therapy investigational medicinal products, specific guidance is contained in the detailed guidelines on good clinical practice specific to advanced therapy medicinal products ⁽¹⁰⁾.

19. Delegation of tasks does not remove the ultimate responsibility of the sponsor or investigator for the conduct of the clinical trial in accordance with the applicable legislation.

4. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

4.1. Legal basis and purpose

20. Article 16(1) of Directive 2001/20/EC reads as follows:

‘The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator’s brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.’

21. The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial, in accordance with Article 3(2)(a) of Directive 2001/20/EC.

4.2. ‘Serious adverse event’

4.2.1. ‘Adverse event’

22. An ‘adverse event’ is defined in Article 2(m) of Directive 2001/20/EC as follows:

‘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’.

23. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product ⁽¹¹⁾.

4.2.2. ‘Serious adverse event’

24. A ‘serious adverse event’ is defined in Article 2(o) of Directive 2001/20/EC as follows:

‘Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect’.

25. These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

26. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition.

27. Medical and scientific judgement should be exercised in deciding whether an event is ‘serious’ in accordance with these criteria ⁽¹²⁾.

4.3. Timelines

28. The investigator has to immediately report to the sponsor all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the investigator’s brochure (‘IB’) ⁽¹³⁾.

4.3.1. Immediate reporting and follow-up report

29. Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.

30. The follow-up report should allow the sponsor to determine whether the serious adverse event requires a reassessment of the benefit-risk balance of the clinical trial, if the relevant information was not already available and provided in the initial report.

4.3.2. Non-immediate reporting

31. In cases where reporting is not required immediately (see above under section 4.3) the investigator shall report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB ⁽¹⁴⁾.

⁽¹⁰⁾ EudraLex, Volume 10.

⁽¹¹⁾ Section 2.A.1 of the note for guidance ICH E2A.

⁽¹²⁾ Examples are provided in section 2.B of the note for guidance ICH E2A.

⁽¹³⁾ See also sections 2.5 and 2.6 of the detailed guidance CT-1.

⁽¹⁴⁾ See footnote 13.

4.4. Start and end of reporting serious adverse events to the sponsor

32. The investigator is responsible for reporting to the sponsor all serious adverse events in relation to subjects treated by him in the clinical trial. The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided otherwise in the protocol ⁽¹⁵⁾.
33. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them ⁽¹⁶⁾.

5. REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE SPONSOR

34. Article 16(2) of Directive 2001/20/EC reads as follows:

‘Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.’

35. Regarding the definition of adverse event, reference is made to section 4.2.1.

6. RECORD-KEEPING BY THE SPONSOR

36. Article 16(4), first sentence of Directive 2001/20/EC reads as follows:

‘The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators.’

7. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE SPONSOR

7.1. Legal basis and purpose

37. Article 17(1)(a), (b) and (d) of Directive 2001/20/EC reads as follows:

‘The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee,

and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor. [...]

The sponsor shall also inform all investigators.’

38. Article 17(3)(a) of Directive 2001/20/EC reads as follows:

‘Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access.’

39. The ‘European database’ referred to in Article 17 of Directive 2001/20/EC is the Eudravigilance Clinical Trials Module (‘EVCTM’) ⁽¹⁷⁾.

40. The purpose of the reporting obligation towards national competent authorities (be it directly or indirectly through EVCTM, see section 7.4) is to make national competent authorities aware of SUSARs and to collect safety information on the safety profile of an IMP. This, in turn, is intended to give the relevant national competent authority the opportunity to:

- assess, in view of the various reported SUSARs, whether an IMP poses an unknown risk to the subject, and
- take measures to protect the safety of subjects, if necessary.

41. The purpose of the reporting obligation towards the Ethics Committee (see section 80) is to make the Ethics Committee aware of SUSARs that have occurred in the territory of the Member State concerned.

42. The purpose of the information obligation towards the investigator (see section 7.10) is to inform investigators of safety issues in view of detected SUSARs.

⁽¹⁵⁾ For advanced therapy medicinal products there are specific provisions in section 8 of the *detailed guidelines on good clinical practice specific for advanced therapy medicinal products* (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm).

⁽¹⁶⁾ See section 3.E.3 of the note for guidance ICH E2A.

⁽¹⁷⁾ <http://eudravigilance.ema.europa.eu/human/index02asp>

7.2. Suspected unexpected serious adverse reaction

7.2.1. 'Adverse reaction' — causality

43. An 'adverse reaction' is defined in Article 2(n) of Directive 2001/20/EC as follows:

'all untoward and unintended responses to an investigational medicinal product related to any dose administered'.

44. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

45. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

46. An untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR (see also section 7.6). For possible follow-up action reference is made to section 7.11.3.

7.2.2. 'Serious' adverse reaction

47. Regarding the criterion of 'seriousness', reference is made to section 4.2.2.

7.2.3. 'Unexpected' adverse reaction

7.2.3.1. Definition

48. Article 2(p) of Directive 2001/20/EC defines 'unexpected adverse reaction' as follows:

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

49. The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious' ⁽¹⁸⁾.

50. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events ⁽¹⁹⁾.

⁽¹⁸⁾ For examples, see section 2.B of the note for guidance ICH E2A.

⁽¹⁹⁾ For examples, see section 2.C.2 of the note for guidance ICH E2A.

7.2.3.2. Reference safety information

51. The expectedness of an adverse reaction is determined by the sponsor in the reference safety information ('RSI'). This should be done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product ⁽²⁰⁾.

52. The RSI is contained in the Summary of product characteristics ('SmPC') or the IB ⁽²¹⁾. The covering letter which is submitted with the application to the national competent authority should refer to the RSI ⁽²²⁾.

53. If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect. This section should include information on the frequency and nature of the adverse reactions.

54. If the IMP has a marketing authorisation in several Member States concerned with different SmPCs, the sponsor should select the most appropriate SmPC, with reference to subject safety, as RSI ⁽²³⁾.

55. The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment ⁽²⁴⁾. For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies ⁽²⁵⁾. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 8.

7.3. Assessment of seriousness, causality and expectedness

56. The sponsor is responsible for ensuring that all adverse events are reported which, cumulatively,

— have a reasonable possibility of a causal relationship (see section 7.2.1) to an IMP,

⁽²⁰⁾ See section 2.C of the note for guidance ICH E2A.

⁽²¹⁾ See section 2.6 of the detailed guidance CT-1 for details.

⁽²²⁾ See section 2.3 of the detailed guidance CT-1 for details.

⁽²³⁾ See footnote 21.

⁽²⁴⁾ See sections 3.3 and 3.4 of the detailed guidance CT-1 for details.

⁽²⁵⁾ See footnote 21.

- are ‘serious’ (see section 7.2.2); and
- are ‘unexpected’ (see section 7.2.3).

7.3.1. ‘Seriousness’

57. The judgement as to whether the event is serious is usually made by the reporting investigator (see section 4.2.2).

7.3.2. Causality

58. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator.
59. In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator’s causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

7.3.3. ‘Expectedness’

60. Assessment of expectedness is usually done by the sponsor.
61. The ‘expectedness’ of a serious adverse reaction is assessed in the light of the RSI (see section 7.2.3.2).
62. If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

7.4. SUSARs reported to the national competent authority (directly or indirectly through EVCTM)

7.4.1. Introduction

63. SUSARs have to be reported to the national competent authority of the Member State concerned.
64. In addition, EVCTM has to be populated with these reports.
65. In the future, in order to simplify workflows and to avoid duplicate populating of EVCTM, the reporting of SUSARs to the national competent authority should be made for all SUSARs through EVCTM. To this end, the capabilities of EVCTM are currently improved in accordance with section 9.3 towards ‘enhanced functionalities’. Once the enhanced functionalities have been reached, a ‘final arrangement’ (see section 7.4.3) applies. Until that time, i.e. during the transitional period, a ‘transitional arrangement’ (see section 7.4.2) applies.
66. The Commission will publicly announce when this final arrangement has been reached, after this has been established jointly by the Commission, the European Medicines Agency (‘Agency’) and the national competent authorities.

67. Regarding reporting to the national competent authority, a distinction has to be made between direct and indirect reporting:

- ‘Direct reporting’: the sponsor reports the SUSAR directly as an individual case safety report (‘ICSR’) to the national competent authority of the relevant Member State ⁽²⁶⁾,
- ‘Indirect reporting’/‘Indirect reporting through EVCTM’: the sponsor reports the SUSAR as an ICSR through EVCTM to the national competent authority of the relevant Member State ⁽²⁷⁾.

7.4.2. SUSARs to be reported and reporting modalities (transitional arrangement)

68. The transitional arrangement (see section 7.4.1) for reporting SUSARs to the national competent authorities is as follows:

7.4.2.1. SUSARs to be reported (transitional arrangement)

69. The sponsor of a clinical trial performed in at least one Member State should report the following SUSARs:
- all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or at a trial site in a third country concerned,
 - all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country or exclusively in another Member State, if that clinical trial, is
 - sponsored by the same sponsor, or
 - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor ⁽²⁸⁾.

⁽²⁶⁾ For details which is the ‘relevant’ Member State, see below.

⁽²⁷⁾ See footnote 26.

⁽²⁸⁾ Provision of the IMP or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.

- 7.4.2.2. Reporting modalities (transitional arrangement)
70. In the transitional arrangement, the modalities for reporting are as follows:
- (a) Reporting to the national competent authority ⁽²⁹⁾:
- The SUSARs referred to in section 7.4.2.1, first bullet, are reported to the national competent authority of every Member State where the national competent authority has authorised the clinical trial.
 - The SUSARs referred to in section 7.4.2.1, second bullet, are reported to the national competent authority of every Member State where the national competent authority has authorised the clinical trial which is performed in the EU.
71. The reporting of SUSARs to the national competent authority starts with the authorisation of the clinical trial by that authority ⁽³⁰⁾. It ends with the completion of the treatment of all subjects enrolled in that Member State.
- (b) Populating EVCTM:
72. The Member State where the SUSAR has occurred is responsible for ensuring that EVCTM is populated with the SUSARs which are reported to its Member State according to this section. To this end the Member State may:
- Provide for the national competent authority to populate EVCTM.
 - Provide for indirect reporting, or
 - Leave it up to the sponsor to choose indirect or direct reporting. In this case, if the sponsor chooses direct reporting it has to be ensured that EVCTM is populated by the national competent authority.
73. If the SUSAR has occurred in a third country, and that clinical trial is performed also in the EU, the sponsor should report indirectly through EVCTM or choose any one Member State where the national competent authority populates EVCTM and where the national competent authority has authorised the clinical trial.
74. If the clinical trial is exclusively performed in a third country, and the SUSAR is reported to the national competent authority of a Member State (see section 7.4.2.1, second bullet), the sponsor should report indirectly through EVCTM or choose any one Member State where the national competent authority populates EVCTM and where the national competent authority has authorised the clinical trial which is performed in the EU.
75. SUSARs identified after the end of the trial ⁽³¹⁾ should be reported as well. This should be done by way of indirect reporting through EVCTM.
- 7.4.3. SUSARs to be reported and reporting modalities (final arrangement)
76. The final arrangement (see section 7.4.1) for reporting SUSARs is as follows:
- 7.4.3.1. SUSARs to be reported (final arrangement)
77. The sponsor of a clinical trial performed in at least one Member State should report the following SUSARs:
- all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or in a third country concerned, and
 - all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country, if that clinical trial, is
 - sponsored by the same sponsor, or
 - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor ⁽³²⁾.
- 7.4.3.2. Reporting modalities (final arrangement)
78. SUSARs to be reported in accordance with section 7.4.3.1 are reported indirectly to the national competent authorities of all Member States concerned through EVCTM.

⁽²⁹⁾ A list of addressees and databases for the national competent authorities is available here: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

⁽³⁰⁾ For SUSARs occurring prior to the authorisation, see section 2.1.4.2. of the detailed guidance CT-1.

⁽³¹⁾ On the notion of 'end of trial', see section 4 of the detailed guidance CT-1.

⁽³²⁾ See footnote 28.

79. Sponsors may not have the resources and experience for indirect reporting. Consequently, the sponsor may:

- where this possibility is provided for by a Member State where the SUSAR has to be reported, make use of direct reporting,
- delegate indirect reporting to another person. For example, where a commercial partner is involved (e.g. the marketing authorisation holder of the IMP), indirect reporting could be delegated to that partner⁽³³⁾.

80. SUSARs identified after the end of the trial⁽³⁴⁾ should be reported as well. This should be done by way of indirect reporting through EVCTM.

7.5. Reporting of SUSARs to the Ethics Committee

81. Ethics Committees do not have access to EVCTM⁽³⁵⁾.

82. Sponsors should report to the Ethics Committee issuing the 'single opinion' in accordance with Article 7 of Directive 2001/20/EC all SUSARs occurring in the clinical trial concerned, if the SUSARs occurred in the territory of that Member State.

83. It is recommended that the Ethics Committee and the national competent authority liaise closely on matters related to subject safety, where necessary.

7.6. Adverse reactions *not* to be reported as SUSARs

84. Sections 7.4 and 7.5 contain an exhaustive list of SUSARs to be reported. In particular, there is no need for the sponsor to report as SUSARs:

- adverse reactions related not to an IMP but to a non-IMP received by the subject and without interaction with the IMP (see section 7.2.1),
- SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. These SUSARs may come to the attention

of the sponsor through individual reports, publications (such as academic literature) or regulatory authorities⁽³⁶⁾,

- adverse reactions occurring in a third country outside a clinical trial in relation to a medicinal product which is marketed there but which is exclusively used as an IMP in the EU.

85. These cases are instead addressed through reporting other than SUSAR reporting, as well as follow-up measures (see sections 7.11.3 and 7.11.4).

86. The rules on pharmacovigilance remain inapplicable in these cases (see section 2).

7.7. Timelines for reporting relevant information on fatal or life-threatening SUSARs

7.7.1. Reporting of 'relevant information'

87. The sponsor must report all information that is 'relevant', i.e. the information which is necessary in order to:

- verify whether the anticipated therapeutic and public health benefits continue to justify the foreseeable risks, and
- process the report administratively.

88. Medical and scientific judgement should be applied in identifying non-relevant and relevant information.

89. In particular, new administrative information that could impact on the case management is to be considered as 'relevant'. One example is information that may help to detect potential duplicates (e.g. new case identifiers have become known to the sponsor which may have been used in previous transmissions).

90. It may transpire, after the initial reporting, that the event is not a SUSAR, for example due to lack of causality, seriousness, or expectedness (hereinafter referred to as 'downgrade'). Downgrades should be considered as relevant information.

91. Examples of non-relevant information are minor changes of dates or corrections of typographical errors in the previous case version.

⁽³³⁾ See section 5.1. of the Clinical Trials Application Form (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm).

⁽³⁴⁾ See footnote 31.

⁽³⁵⁾ Article 17(3)(a) of Directive 2001/20/EC.

⁽³⁶⁾ Reporting these SUSARs would lead to double-entries as, in a functioning system, those SUSARs would be reported anyway.

- 7.7.2. *Timelines, clock-start*
92. In applying the rules on reporting of relevant information within the timelines the following should apply:
93. The clock for expedited initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor ⁽³⁷⁾.
94. For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case.
95. If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor is to submit a completed report based on the initial information within an additional eight days. In this instance, the receipt date should not be changed with regard to the initial report ⁽³⁸⁾.
96. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days ⁽³⁹⁾.
97. The minimum information includes, at least, all of the following:
- valid EudraCT number (where applicable) ⁽⁴⁰⁾,
 - sponsor study number ⁽⁴¹⁾,
 - one identifiable coded subject ⁽⁴²⁾,
 - one identifiable reporter ⁽⁴³⁾,
- one SUSAR ⁽⁴⁴⁾,
- one suspect IMP (including active substance name-code) ⁽⁴⁵⁾,
- a causality assessment ⁽⁴⁶⁾.
98. In addition, in order to properly process the report electronically, the following administrative information should be provided:
- the sender's (case) safety report unique identifier ⁽⁴⁷⁾,
 - the receive date of the initial information from the primary source ⁽⁴⁸⁾,
 - the receipt date of the most recent information ⁽⁴⁹⁾,
 - the worldwide unique case identification number ⁽⁵⁰⁾,
 - the sender identifier ⁽⁵¹⁾.
99. For the format and structure of the information, see section 7.9.

7.8. Timelines for non-fatal and non-life-threatening SUSARs

100. SUSARs which are not fatal and not life-threatening are to be reported within 15 days.
101. There may be cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening. The non-fatal or non-life-threatening SUSAR should be reported as soon as possible, but within 15 days. The fatal or life-threatening SUSAR follow-up report should be made as soon as possible, but within a maximum of seven days after first knowledge of the reaction being fatal or life-threatening. Regarding the follow-up report, see section 7.7.2.

⁽³⁷⁾ If the task has been delegated to another person, the date of receipt by that other person is the clock-start.

⁽³⁸⁾ In case of electronic transmission of the ICSR, this means that the date specified in the ICH E2B(R2) data element A.1.6 'Receive date' should be the same as the date specified in the ICH E2B(R2) data element A.1.7 'Receipt date'.

⁽³⁹⁾ In case of electronic transmission of the ICSR this means that the date specified in the ICH E2B(R2) data element A.1.6 'Receive date' should be the same as the date when the initial report was received. In the ICH E2B(R2) data element A.1.7 'Receipt date' the date when significant new information on the case was received by the sponsor should be indicated.

⁽⁴⁰⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.2.3.1.

⁽⁴¹⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.2.3.2.

⁽⁴²⁾ For electronic transmission to be included in the ICH E2B(R2) Section B.1.

⁽⁴³⁾ For electronic transmission to be included in the ICH E2B(R2) Section A.2.

⁽⁴⁴⁾ For electronic transmission to be included in the ICH E2B(R2) Section B.2.

⁽⁴⁵⁾ For electronic transmission to be included in the ICH E2B(R2) Section B.4.

⁽⁴⁶⁾ For electronic transmission to be included in the ICH E2B(R2) Section B.4.k.18.

⁽⁴⁷⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.1.0.1.

⁽⁴⁸⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.1.6.

⁽⁴⁹⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.1.7.

⁽⁵⁰⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.1.10.

⁽⁵¹⁾ For electronic transmission to be included in the ICH E2B(R2) data element A.3.1.2.

102. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, while the initial report has not yet been submitted, a combined report should be created.

7.9. Format of report

7.9.1. In case of indirect reporting

103. Regarding the details of reporting indirectly an individual case safety report (ICSR) through EVCTM, reference is made to the following documents:

- the current version of the ICH E2B guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (hereinafter 'ICH E2B(R2)')⁽⁵²⁾, and
- The current version of the Note for guidance EudraVigilance Human — Processing of safety messages and individual case safety reports (ICSRs)⁽⁵³⁾.

104. It should be emphasised that:

- the sponsor should provide, before completing the clinical trials application form⁽⁵⁴⁾, information on the IMP in the EudraVigilance Medicinal Product Dictionary (EVMPD)⁽⁵⁵⁾,⁽⁵⁶⁾,
- the data in free-text fields should be entered in English,
- only reports complying with the validation rules⁽⁵⁷⁾ are accepted in EVCTM,
- the data in coded fields should contain internationally agreed terminologies, formats and standards for the conduct of pharmacovigilance.

⁽⁵²⁾ <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

⁽⁵³⁾ Doc. Ref. EMA/H/20665/04/Final Revision 2 of 15 October 2010 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800250b3).

⁽⁵⁴⁾ http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

⁽⁵⁵⁾ In order to standardise information between clinical trial applications and related SUSARs reported to the competent authorities, a list of all active substances entered in the EudraVigilance Medicinal Product Dictionary, including development substances — codes, will be made available in the public domain for use in completing the clinical trial application form for EudraCT in the relevant fields.

⁽⁵⁶⁾ A 'help function' will be available by the Agency for sponsors who have difficulty with accessing or entering information in EVMPD.

⁽⁵⁷⁾ See Note for guidance EudraVigilance Human — Processing of safety messages and individual case safety reports (ICSRs), Doc. Ref. EMA/H/20665/04/Final Revision 2 of 15 October 2010.

105. Regarding initials or names of persons, if these are known to the sender but cannot be reported due to personal data protection requirements, this should be highlighted in the report⁽⁵⁸⁾.

7.9.2. In case of direct reporting

106. The information should be structured in the same way as for indirect reporting, to enable the national competent authority to populate EVCTM.

107. This should also apply during the transitional arrangement referred to in section 7.4.2.

7.10. Informing the investigator

108. Article 17(1)(d) of Directive 2001/20/EC provides that 'the sponsor shall also inform all investigators'.

109. The information should be concise and practical. Therefore, whenever practicable the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/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 IMP.

110. Regarding blinded treatment allocation, see section 7.11.1.

7.11. Other issues

7.11.1. Unblinding treatment allocation⁽⁵⁹⁾

111. As a general rule only SUSARs on which the treatment allocation of the subject is unblinded should be reported by the sponsor to the national competent authority (be it directly or indirectly through EVCTM, see section 7.4), as well as the Ethics Committee (see section 7.5).

112. Investigators (see section 7.10) should only receive blinded information unless unblinded information is judged necessary for safety reasons⁽⁶⁰⁾.

113. The investigator should only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the subject.

⁽⁵⁸⁾ As regards the ICH E2B data elements, the field should be populated by 'PRIVACY'.

⁽⁵⁹⁾ See also section 3.D. of the note for guidance ICH E2A.

⁽⁶⁰⁾ More information is contained in section 3.D of the note for guidance ICH E2A.

114. As regards the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific subject. The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information should only be accessible to those who need to be involved in the safety reporting to national competent authorities (be it directly or indirectly through EVCTM), Ethics Committees and Data Safety Monitoring Boards ('DSMB')⁽⁶¹⁾, or persons performing ongoing safety evaluations during the trial.

115. However, for trials in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another 'serious' outcome (that may potentially be reported as a SUSAR) is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor should reach agreement in the authorisation process as to which serious events would be treated as disease-related and not subject to systematic unblinding and expedited reporting⁽⁶²⁾.

116. For such trials, sponsors are strongly encouraged to appoint an independent DSMB in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of the DSMB should be described in the protocol.

117. In all cases, following unblinding, if the event turns out to be a SUSAR (for example as regards expectedness), the reporting rules for SUSARs apply (see sections above). For cases where the SUSAR becomes apparent only after the trial has ended, reference is made to section 7.4.

7.11.2. SUSARs associated with active comparator or placebo

118. Comparators and placebos are IMPs⁽⁶³⁾. Therefore, SUSARs associated with a comparator product follow the same reporting requirements as for the test IMP. Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore for expedited

reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient or impurity), the sponsor should report such cases⁽⁶⁴⁾.

7.11.3. Adverse reactions related to non-IMPs

119. A serious adverse reaction which is related not to an IMP but to a non-IMP is not a SUSAR and not reported as such (see section 7.2.1).

120. While the legal obligations contained in the rules on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply (see section 2) to adverse reactions to IMPs or non-IMPs, in cases where the non-IMP is an authorised medicinal product, investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to national competent authorities or to the marketing authorisation holder.

7.11.4. Safety issues not falling within the definition of SUSAR — other measures

121. Events may occur during a clinical trial which do not fall within the definition of SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples⁽⁶⁵⁾ are:

- new events related to the conduct of a trial or the development of an IMP likely to affect the safety of 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),

- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,

⁽⁶¹⁾ On DSMBs, see also the EMA guideline on Data Monitoring Committees, Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr (<http://www.ema.europa.eu/pdfs/human/ewp/587203en.pdf>).

⁽⁶²⁾ See section 2.5 of the detailed guidance CT-1.

⁽⁶³⁾ Article 2(d) of Directive 2001/20/EC.

⁽⁶⁴⁾ The suspected ingredient of the placebo should be specified in the ICH E2B(R2) data element B.4.k.2.2. 'Active substance name'.

⁽⁶⁵⁾ For examples, see section 3.A.2 of the note for guidance ICH E2A.

- recommendations of the DSMB, if any, where relevant for the safety of subjects,
- in the case of advanced therapy investigational medicinal products, relevant safety information regarding the procurement or the donor.

122. These events/observations are not to be reported as SUSARs, but they might require other action, such as:

- urgent safety measures and their notification (Article 10(b) of Directive 2001/20/EC, see also section 3.9 of the detailed guidance CT-1),
- substantial amendments (Article 10(a) of Directive 2001/20/EC; see also section 3.7 of the detailed guidance CT-1), or
- early termination of the trial (Article 10(c) of Directive 2001/20/EC; see also section 4.2.2 of the detailed guidance CT-1).

123. Moreover, it is recommended that the sponsor informs the national competent authority and the Ethics Committee of safety issues which might materially alter the current benefit-risk assessment of an IMP while not falling within the actions listed above.

8. ANNUAL SAFETY REPORTING BY THE SPONSOR TO THE NATIONAL COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

124. Article 17(2) of Directive 2001/20/EC reads as follows:

‘Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects’ safety.’

125. The report is addressed to the national competent authority and the Ethics Committee of the Member State concerned.

126. The report should only be submitted to the national competent authority and the Ethics Committee if the treatment of subjects is still ongoing in that Member State concerned ⁽⁶⁶⁾.

127. For details regarding annual safety reporting, including rules for unblinding, reference is made to the guideline ICH Topic E2F — Development Safety Update Report ⁽⁶⁷⁾ (‘DSUR’, hereinafter ‘note for guidance ICH E2F’). The

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published ‘model DSURs’. These ‘model DSURs’ take account of the differing knowledge about a medicine, depending on whether the sponsor holds the marketing authorisation or not ⁽⁶⁸⁾.

128. The report should contain, in an appendix, the RSI in effect at the start of the reporting period (see section 7.2.3.2; see also sections 2.6 and 3.20 of the note for guidance ICH E2F).

129. The RSI in effect at the start of the reporting period serves as RSI during the reporting period ⁽⁶⁹⁾.

130. If there are significant changes to the RSI during the reporting period they should be listed in the annual safety report ⁽⁷⁰⁾, ⁽⁷¹⁾. Moreover, in this case the revised RSI should be submitted as an attachment to the report ⁽⁷²⁾, in addition to the RSI in effect at the start of the reporting period (see above). Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period ⁽⁷³⁾.

9. FUNCTIONALITIES OF EVCTM

9.1. Introduction

131. EVCTM serves the following purposes:

- provision of an overview of SUSARs relevant for supervising clinical trials in the EU as a whole and in each Member State,
- facilitation of reporting to the national competent authorities by way of indirect reporting, in particular in the case of multinational trials,
- facilitation of communication of SUSARs between national competent authorities, the Commission and the Agency.

⁽⁶⁸⁾ <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

⁽⁶⁹⁾ See section 2.6 of the note for guidance ICH E2F.

⁽⁷⁰⁾ See section 3.4 of the note for guidance ICH E2F.

⁽⁷¹⁾ They are typically also substantial amendments, see section 3.4.3.b of the detailed guidance CT-1.

⁽⁷²⁾ See footnote 69.

⁽⁷³⁾ This means that the RSI used as the basis for the annual report may not be identical with the evolving RSI which is the basis for SUSAR reporting (see section 7.2.3.2).

⁽⁶⁶⁾ See section 2.3 of the note for guidance ICH E2F.

⁽⁶⁷⁾ http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

132. The data contained in EVCTM are not accessible to persons other than the national competent authorities, the Agency and the Commission ⁽⁷⁴⁾.

133. EVCTM is based on pick lists, dropdown menus and dictionaries or automatically generated codes or text. It is acknowledged 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.

9.2. Basic functionalities

134. The basic functionalities of EVCTM allow for:

- indirect reporting based on the current version of internationally agreed formats,
- generating specific reports integrating statistical methods of signal detection with option of primary filtering on source country, type of report, drug characterisation, the number of the European clinical trials database EudraCT (EudraCT number), sending organisations (national competent authorities, sponsors), date of reporting,
- Querying for:
 - number of SUSARs reported for one or more selected IMPs or active substances,
 - number of SUSARs reported by age group or indication (if reported) for one or more selected IMPs or active substances,

- number of SUSARs reported for a selected clinical trial based on one or more EudraCT numbers,

- individual case line listings for reactions grouped at any level of the MedDRA hierarchy for one or more selected medicinal products or active substances,

- Static reaction monitoring reports for one or more selected medicinal products or active substances.

9.3. Enhanced functionalities

135. After the transitional arrangement (section 7.4.1), EVCTM will have enhanced functionalities in conjunction with EudraCT, allowing national competent authorities to receive:

- regular messages on new SUSARs for all relevant IMPs/clinical trials,
- alerts in respect of SUSARs relevant to Member States for certain types of reactions, trials or populations, or IMPs of interest, and
- reports based on a range of ICH E2B and EudraCT fields.

136. Detailed technical requirements, as well as an implementation plan for the enhanced functionalities, are going to be published in a separate document.

⁽⁷⁴⁾ See Article 17(3)(a) of Directive 2001/20/EC.