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PUBLIC CONSULTATION DOCUMENT
Draft detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ('CT-3')

This draft is a revision of the existing detailed guidance of the Commission on adverse reaction reporting, including SUSAR reporting. Once published, this document will replace the following documents:

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

- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical Trial Module); and

- Questions & Answers specific to adverse reaction reporting in clinical trials.

The draft revised document is herewith submitted for public consultation. All stakeholders are invited to comment. Stakeholders who are not established within the European Union are likewise invited to comment.

This initiative is a response to many calls from stakeholders during the *public consultation on the functioning of the Clinical Trials Directive*[1] for short-term improvements/clarifications of the detailed rules for safety reporting. These improvements have to be limited to what is possible under the current legal framework. The *revision of the Clinical Trials Directive*[2] is a medium/long-term project, conducted in parallel to this public consultation and aiming at more structural improvements of the situation for investigators and sponsors.

Despite the scope of this public consultation being limited to the existing legal framework (ie the Clinical Trials Directive 2001/20/EC), respondents may wish to profit from this consultation to comment also on more structural issues regarding safety-reporting which would have to be considered in the abovementioned revision of the Clinical Trials Directive.

Contributions should be sent by e-mail to sanco-pharmaceuticals@ec.europa.eu by 10 September 2010 at the latest.

Contributions will be made publicly available on the 'Clinical Trials' website of the Commission once the consultation period is over. If you do not wish your contribution to be made public, please indicate this clearly and specifically in the submitted documentation. In such a case, only the name of the contributor will be disclosed.

1 http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm
2 http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm

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[3] (hereinafter 'Directive 2001/20/EC'), which lays down the following:

'*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 requirements as regards clinical trials have to be consistent with the procedures and time-scales set out in Directive 2001/20/EC, such as the 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. EU Member States, Contracting States of the European Economic Area ('EEA'),[4] sponsors, persons to whom the sponsor has delegated tasks and functions related to collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (hereinafter referred to as 'delegated person'), as well as investigators, should consider this guidance when applying Directive 2001/20/EC.

1.2. Scope

4. The scope of this detailed guidance is the scope of Directive 2001/20/EC, i.e. clinical trials as defined in Directive 2001/20/EC and performed in at least one Member State of the Union.

5. For more details on the scope of Directive 2001/20/EC reference is made to the *Detailed guidance for 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*[5] (hereinafter referred to as 'detailed guidance CT-1').

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3 OJ L 121, 1.5.2001, p. 34.

4 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.

5 OJ, C 82, 30.3.2010, p. 1.

1.3. Definitions

6. The definitions contained in Directive 2001/20/EC, its implementing acts and relevant guidance documents in the current version also apply in respect of this guidance.

7. With regard to implementing guidelines, the following guidance documents in particular provide valuable additional definitions:

- *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials* (on the term 'investigational medicinal products');[6] and
- *Questions and Answers Document on the Clinical Trials Directive*.[7]

8. Regarding the definitions of the terms 'adverse event', 'adverse reaction', 'suspected', 'unexpected', and 'serious', reference is made to the respective sections in this detailed guidance.

9. For the purposes of this detailed guidance, 'Member State concerned' means the Member State in which the clinical trial has obtained authorization from the national competent authority, as well as the favourable opinion of the Ethics Committee.

2. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR

2.1. Legal basis and purpose

10. 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.*'

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

2.2. 'Serious adverse event'

12. 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,*

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6 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm.

7 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm.

results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect'.

2.2.1. 'Adverse event'

13. The term 'adverse event' is further discussed in the *Note for guidance on clinical safety management: Definition and standards for expedited reporting*[8] (hereinafter referred to as 'note for guidance ICH E2A').

2.2.2. 'Serious event'

14. An adverse event is 'serious' if it has the following characteristics/consequences:

- it results in death;
- it is life-threatening;
- it requires hospitalisation or prolongation of existing hospitalisation;
- it results in persistent or significant disability or incapacity; or
- it is a congenital anomaly or birth defect.

15. These characteristics/consequences have to be considered at the time of the event.

16. Medical events may jeopardise the clinical trial participant or may require an intervention to prevent one of the characteristics/consequences above. Those events (hereinafter referred to 'important medical events') should also be considered as 'serious' in accordance with the definition.

17. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria. Examples are provided in the note for guidance ICH E2A.

2.3. Extent and timelines

18. The investigator has to immediately report 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').[9]

2.3.1. Immediate reporting and follow-up report

19. The 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 within a very short period of time and under no circumstances exceed 48 hours following knowledge of the adverse event.

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8 CPMP/ICH/377/95, http://www.ema.europa.eu/pdfs/human/ich/037795en.pdf

9 Cf. also Section 2.5. and 2.6. of the detailed guidance CT-1.

20. The follow-up report should allow the sponsor to assess in detail whether the adverse event requires a reassessment of the risk-benefit balance of the clinical trial, if those details were not already available and provided in the initial report.

2.3.2. Non-immediate reporting

In cases where reporting is not required immediately (see section 2.3) the investigator shall report within the appropriate timeframe taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the IB.

2.4. Subject identification

21. In the report, the subject shall be identified by way of unique code numbers assigned to him.

3. REPORTING OF NON-SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR

22. 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.'

23. Regarding the definition of adverse event, reference is made to section 2.2.1.

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

4.1. Legal basis, purpose

24. Article 17(1),(3) of Directive 2001/20/EC establishes the rules for reporting of suspected unexpected serious adverse reactions ('SUSARs') by the sponsor.

25. The purpose of these reporting obligations is to make regulators aware of SUSARs (cf. chapter 2C of the note for guidance E2A). This, in turn, is intended to give the relevant national competent authority and the Ethics Committee the possibility to

- take measures to protect the safety of clinical trial participants; and
- assess, in view of the various reported SUSARs, whether an IMP poses an unknown risk to the clinical trial participant.

4.2. Suspected unexpected serious adverse reaction

4.2.1. 'Adverse reaction' - causality

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

'A*ll untoward and unintended responses to an investigational medicinal product related to any dose administered*'.

27. Thus, the definition of ‘adverse reaction’ includes causality between the event and the IMP.

28. An untoward and unintended response to a non-IMP (e.g. concomitant medications, background treatments, rescue medications or challenge agents) which does not result from an interaction with an IMP is, by definition, not a SUSAR.

29. In some cases it may be difficult to establish causality. On this aspect, reference is made to section 4.3.2.

4.2.2. ‘Serious’ adverse reaction

30. Regarding the criterion of ‘seriousness' reference is made to section 2.2.2.

4.2.3. ‘Unexpectedness’

31. Article 2(p) of Directive 2001/20/EC defines ‘unexpected adverse reaction’ as follows:

32. *‘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)’.*

33. The term ‘severe’ is used here to describe the intensity (severity) of a specific event. This has to be distinguished from the term ‘serious’. More guidance on the difference is contained in chapter 2B of the note for guidance ICH E2A.

34. The unexpectedness of an adverse reaction is determined by the sponsor according to the reference safety information. In this respect, reference is made to the detailed guidance CT-1.

4.2.4. SUSARs occurring after the end of the trial

35. The definition of SUSAR is independent of whether the clinical trial has ended (‘post-study SUSAR’) or is still ongoing. The obligations related to SUSAR reporting do not finish with the end of the trial.

4.3. Assessment of seriousness, causality and unexpectedness

4.3.1. ‘Seriousness’

36. The sponsor is responsible for ensuring that the reported reaction is serious. This judgement is usually delivered by the reporting investigator (see section 2.2.2).

4.3.2. Causality

37. The sponsor is responsible for ensuring that only adverse reactions, i.e. causal events, are reported.

38. On the other hand, it is acknowledged that in some cases it is difficult to establish with absolute certainty that an event is causal.

39. To avoid over-reporting while, at the same time, ensuring that relevant events are reported, a 'reasonable causal relationship' should suffice. Chapter 3A1 of the note for guidance ICH E2A provides further information on the terms and scales used in this respect.

40. The assessment of causality is often made by the investigator. On the role of the investigator's assessment of the causality, reference is made to chapter 3A1 of the note for guidance ICH E2A.

41. In the absence of information on the causality by 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, both, the opinion of the investigator and the sponsor should be provided with the report.

4.3.3. Expectedness

42. The sponsor is responsible for ensuring that only unexpected adverse reactions are reported.

43. The 'expectedness' of a serious adverse reaction is assessed in the light of the applicable product information (e.g. IB or SmPC).

44. If information on the expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

45. In the absence of information on the expectedness by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. The expectedness assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's expectedness assessment, both, the opinion of the investigator and the sponsor should be provided with the report.

4.4. SUSARs to be reported

46. The sponsor of a clinical trial performed in at least one Member State has to report the following SUSARs of which he obtains knowledge:

- all SUSARs occurring in that clinical trial. This is independent of whether the SUSAR has occurred in a trial site in a Member State or in a third country concerned; and

- all SUSARs related to the same active substance (independent of pharmaceutical form and strength) 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 holds a development agreement with the sponsor.

47. While the transitional reporting procedures still apply, additional SUSARs should be reported to Member States (cf. Section 4.7.3.3).

4.5. Adverse reactions *not* to be reported

48. It follows from section 4.4 that there is no need for the sponsor to report:

- Adverse reactions not related to the IMP but to a non-IMP received by the subject and without interaction with the IMP: This is addressed through the reporting and follow-up measures outside SUSAR reporting (see section 4.2.1); or

- 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 knowledge of the sponsor through spontaneous reports, publications (such as academic literature), or regulatory authorities.[10]

4.6. Interface with safety reporting of authorised medicines under pharmacovigilance rules

49. The reporting obligations under the provisions on pharmacovigilance for authorised medicinal products are set out 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[11] (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 authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (hereinafter 'Regulation 726/2004').[12]

50. For details, reference is made to the guidelines published in Volume 9 of *EudraLex — The Rules Governing Medicinal Products in the European Union*.[13]

51. Safety reporting falls *either* under Directive 2001/20/EC *or* under the provisions on pharmacovigilance as set out in Directive 2001/83/EC. Adverse reactions may not be reported under both regimes, i.e. Directive 2001/20/EC and Regulation 726/2004, Directive 2001/83/EC.

52. An adverse reaction occurring in a clinical trial is only to be reported in accordance with Directive 2001/20/EC and should comply with this detailed guidance.

4.7. Reporting of fatal or life-threatening SUSARs to the national competent authority

53. Article 17(1)(a) of Directive 2001/20/EC reads as follows:

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[10] Reporting these SUSARs would lead to double-entries as, in a functioning system, those SUSARs would be reported anyway.

[11] OJ L 311, 28.11.2001, p. 67.

[12] OJ L 136, 30.4.2004, p. 1.

[13] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3_en.htm.

'*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.*'

54. 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.*'

55. The 'European database' referred to in this Article is the 'Eudravigilance Clinical Trials Module' ('EVCTM').

4.7.1. Initial reporting

4.7.1.1. Timelines, clock-start

56. Initial reporting is to be done within seven days after knowledge by the sponsor of a SUSAR. The clock for expedited reporting of initial report (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the sponsor or the delegated person.

4.7.1.2. Content of initial reporting

57. The sponsor shall 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 risks; and
- process the report administratively.

58. Non-relevant information does not require reporting.

59. Medical judgement should be applied as regards the identification of non-relevant and relevant information.

60. Relevant information includes, at least, the following information:

– Valid EudraCT number;[14]

– Sponsor study number;[15]

– One identifiable coded subject;[16]

[14] For electronic transmission in ICH E2B(R2): data element A.2.3.1.

[15] For electronic transmission in ICH E2B(R2): data element A.2.3.2.

– One identifiable reporter;[17]

– One SUSAR;[18]

– One suspect IMP.[19]

61. In addition, in order to properly process the report, the following administrative information should be provided:

– The sender's (case) safety report unique identifier;[20]

– The receipt date of the initial information from the primary source;[21]

– The receipt date of the most recent information;[22]

– The worldwide unique case identification number;[23]

– The sender identifier.[24]

62. Any one of several data elements is considered sufficient to define an identifiable subject (e.g. code number, initials, age, sex) or an identifiable reporter (e.g. initials, address, qualification).

4.7.2. Follow-up information

4.7.2.1. Timelines

(1) Follow-up information received before the 15 days reporting timeline

63. Relevant follow-up information is to be communicated within an additional eight days.

64. For the start of the clock, see above section 4.7.1.1.

(2) Follow-up information received after the 15 days reporting timeline

65. There may be cases where the sponsor does not obtain knowledge of relevant new information about a SUSAR until after the 15 days referred to in section 4.7.2 have elapsed.

66. In these cases, the clock starts again at day zero, i.e. at the date of the receipt of new information. This information should be reported as a follow-up report within 15 days.

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16 For electronic transmission in ICH E2B(R2): Section B.1.
17 For electronic transmission in ICH E2B(R2): Section A.2.
18 For electronic transmission in ICH E2B(R2): Section B.2.
19 For electronic transmission in ICH E2B(R2): Section B.4.
20 For electronic transmission in ICH E2B(R2): data element A.1.0.1.
21 For electronic transmission in ICH E2B(R2): data element A.1.6.
22 For electronic transmission in ICH E2B(R2): data element A.1.7.
23 For electronic transmission in ICH E2B(R2): data element A.1.10.
24 For electronic transmission in ICH E2B(R2): data element A.3.1.2.

4.7.2.2. Content of reporting of follow-up information

67. The follow-up information has to relate to relevant information. In this respect, reference is made to section 4.7.1.2.

68. 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).

69. 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.

70. Examples of non-relevant information are minor changes of dates (e.g. the day of the birth date) or corrections of typographical errors in the previous case version. Medical judgment should be applied, as a change to the birth date may constitute a relevant change (e.g. it may have implications for the age information of the patient).

4.7.3. Addressee of report, reporting to EVCTM, reporting arrangements

4.7.3.1. Introduction

71. The addressee of the SUSAR report is the national competent authority of the Member State(s) concerned.

72. In addition, EVCTM has to be provided with this report.

73. EVCTM will be the transmission tool for reporting of SUSARs to the Member States concerned. To this end, the capabilities of EVCTM are currently improved in accordance with section 6.2 of this detailed guidance towards 'enhanced functionalities'. Once the enhanced functionalities have been reached, which will be established by the Commission, following consultation of the European Medicines Agency ('Agency') and national competent authorities, section 4.7.3.2 applies. Until that time, i.e. during the transitional period, the reporting modalities set out in section 4.7.3.3 apply.

4.7.3.2. Reporting modalities and use of the European database – direct and indirect reporting

74. SUSARs to be reported in accordance with section 4.4 are reported to all Member States concerned through EVCTM.

75. As regards the input of information regarding SUSARs into EVCTM, Member States may provide for one of the following measures:

- obliging the sponsor to report directly as individual case safety report (‘ICSR’) to EVCTM only (hereinafter referred to as ‘direct reporting’). The national competent authority of the Member State concerned is then informed through EVCTM;

- obliging the sponsor to report only to the national competent authority of the Member State where the SUSAR occurred who, in turn, enters this information into EVCTM (hereinafter referred to as 'indirect reporting'); or

- leaving it up to the sponsor to choose direct or indirect reporting.

76. Sponsors may not have the resources and experience for direct reporting. In order to address this matter, the sponsor may:

- where this possibility is provided for by the Member State concerned, use the possibility of indirect reporting;

- where a commercial partner is involved (e.g. the marketing authorization holder of the IMP), delegate the direct submission to the partner; or

- delegate direct reporting to another person (outsourcing).

4.7.3.3. Transitional reporting procedures

77. With reference to section 4.7.3.1, the following transitional reporting procedures apply:

(1) Reporting to Member States:

- The SUSARs referred to in Section 4.4, 1st bullet, are reported to every Member State concerned;

- The SUSARs referred to in Section 4.4, 2nd bullet, are reported to every Member State where the same sponsor conducts a clinical trial with the same active substance of the IMP (independent of pharmaceutical form and strength).

78. In addition to the SUSARs to be reported in accordance with section 4.4, sponsors should report SUSARs related to the same active substance of the IMP (independent of pharmaceutical form and strength) in a clinical trial performed 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 holds a development agreement with the sponsor.

(2) Reporting to EVCTM:

79. The Member State concerned where the SUSAR occurred is in charge of ensuring that the SUSAR is reported to EVCTM through direct or indirect reporting.

80. If the SUSAR occurred in a third country, and that clinical trial is performed also in the EU, the sponsor should directly report to ECVTM or chose any one Member State concerned which ensures indirect reporting.

81. If the clinical trial is exclusively performed in a third country, and the SUSAR is reported to a Member State (see above), the sponsor should directly report to ECVTM or choose any one Member State which ensures indirect reporting.

4.7.4. Format of report

4.7.4.1. In case of direct reporting

82. Regarding the details of reporting ICSRs to EVCTM, reference is made to the following documents:

- The current version of *ICH Topic E2B - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*;[25] and
- The current version of the *note for guidance Eudravigilance human – processing of safety messages and individual case safety reports (ICSRs)*.[26]

83. It should be emphasized that:

- the sponsor should provide information on the IMP in the EudraVigilance Medicinal Product Dictionary;[27] and
- the data in free-text fields should be entered in English.

4.7.4.2. In case of indirect reporting

84. The information should follow the structure as provided for direct submission, in order for the national competent authority to enter the data into EVCTM.

85. This should also apply during the transitional period referred to in section 4.7.3.3.

4.8. Reporting of non fatal and non life-threatening SUSARs to the national competent authority

86. According to Article 17(1)(a) of Directive 2001/20/EC, all other than fatal and non-life-threatening SUSARs '*shall be reported […] as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor*.'

87. Regarding the notion of 'knowledge by the sponsor', the addressee of the report, and the modalities of transmission, reference is made to the sections above (4.7.1.1 and 4.7.3).

88. There may be cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was not considered as fatal or life-threatening. The fatal or life threatening follow-up report should be reported by the sponsor or delegated person

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25 http://www.emea.europa.eu/pdfs/human/ich/028795en.pdf

26 Doc. Ref. EMEA/H/20665/04/Final Revision 1 of 11 November 2009.

27 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 EduraCT in the relevant fields.

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 4.7.2.

4.9. Reporting of SUSARs to Ethics Committees

89. Regarding all aspects of SUSAR reporting (reporting procedures, timelines) reference is made to sections 4.7.1, 4.7.2, 4.7.4.2 and 4.8. Regarding the addressee, this should be only the Ethics Committee issuing the 'single opinion' in accordance with Article 7 of Directive 2001/20/EC of the Member State where the event occurred.

4.10. Informing the investigator

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

91. If appropriate, the information on SUSARs should 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 IMP.

4.11. Other issues

4.11.1. Blinded IMPs[28]

92. Guidance on managing Blinded Therapy Cases is contained in chapter 3D of the note for guidance ICH E2A.

93. As regards the investigator, he should only unblind an IMP in the course of a clinical trial if this is relevant to the safety of the clinical trial participant.

94. As regards the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific patient. The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the study 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 EVCTM, national competent authorities, investigators, ethics committees and Data Safety Monitoring Boards[29], or persons performing ongoing safety evaluations during the trial.

95. 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 endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically

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[28] See also: Chapter D of *ICH Topic E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* http://www.ema.europa.eu/pdfs/human/ich/037795en.pdf

[29] On DSMBs, see also the EMA guideline on Data Monitoring Committees (http://www.ema.europa.eu/pdfs/human/ewp/587203en.pdf).

broken. Under these and similar circumstances, it may be appropriate to reach agreement in the authorisation process which serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting.

96. For such trials, sponsors are strongly encouraged to appoint an independent Data Monitoring Committee 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 a Data Monitoring Committee must be described in the protocol.

97. Following unblinding, if the event turns out to be a SUSAR, 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 4.2.4.

4.11.2. SUSARs associated with active comparator or placebo

98. Comparators and placebos are IMPs. 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 serious adverse drug reaction 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.

4.11.3. Safety issues not falling within the definition of SUSAR – other follow-up measures

99. Events may occur during a clinical trial which do not fall within the reporting requirements of this guideline, even though they may be relevant in terms of patient safety. One example is an adverse reaction which is related not to an IMP but to a Non-IMP (see also section 4.2.1).

100. Moreover, there may be other observations during a clinical trial which may require action to protect the safety of the subjects (for examples, see chapter 3.A.2 of the note for guidance ICH E2A).

101. These events/observations are not to be reported as SUSARs according to this detailed guidance. However, these events/observations might require other action, such as

- notification of urgent safety measures
- a substantial amendment; or
- an early termination of the trial.

102. In this respect, reference is made to the detailed guidance CT-1.

5. YEARLY REPORTING OF SUSPECTED SERIOUS ADVERSE REACTIONS BY THE SPONSOR

103. 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.*'

104. The addressee of the report is the national competent authority and the Ethics Committee of the Member State concerned.

105. For details regarding yearly safety reporting, reference is made to the guideline *ICH Topic E2F – Development Safety Update Report.*

Note to reader: The public consultation on this ICH guideline had been closed in December 2008.[30] The guideline has been finalised. The guideline is going to be signed-off by all ICH countries shortly.

6. FUNCTIONALITIES OF EVCTM

6.1. Introduction

106. EVCTM serves the following purposes:

- Provision of an overview of SUSAR relevant for supervising clinical trials in the Union as a whole and in each Member State;
- Facilitation of the reporting to the national competent authorities of the Member States concerned, in particular in the case of multinational trials;
- Facilitation of communication of SUSARs between national competent authorities, the Commission and the Agency.

107. 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.

6.2. Basic functionalities

108. The basic functionalities of EVCTM allow for:

- Direct reporting based on the internationally agreed formats (i.e. the current version of ICH E2B, ICH M1 MedDRA and ICH M2);
- Generating specific reports integrating traditional and quantitative statistical methods of signal detection with option of primary filtering on source country, type of report, drug characterisation, EudraCT number, sending organisations (national competent authorities, sponsors), date of reporting;

[30] http://www.ema.europa.eu/pdfs/human/ich/30934808en.pdf

- Querying for

– Number of adverse reactions reported for one or more selected medicinal products or active substances;

– Number of adverse reactions reported by age group or indication for one or more selected medicinal products or active substances;

– Number of adverse reactions reported for a selected clinical trial based on the EudraCT number;

– 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.

6.3. Enhanced functionalities

109. After the transitional phase (section 4.7.3.3), EVCTM is going to have the following enhanced functionalities

(1) Daily messages in opening screen of EV-CTM for new SUSARs for all IMPs/clinical trials relevant for Member States. The daily messages should:

– Provide information on suspect or interacting active substance (IMP), EudraCT Number, country of origin, date, initial or follow-up report, special populations, first-in-human, suspect reaction;

– Prioritise by 7 or 15 day reports;

– Keep history for 7 days, update daily;

– Provide hyperlinks to case folders in database;

– Be subject to customisation via front screen elements through use of filters etc.

(2) Alerts of SUSARS relevant for Member States for certain types of reaction (fatal reactions, pancytopenia, hepatic necrosis, QT prolongation) some trials or populations, FIH, healthy volunteers, children, active substance (IMP) of interest.

(3) Reports based on a range of E2B fields including date range; population (age, sex); Member State where the SUSARs occurred; sponsor; active substance; IMP; Reaction; Disease; EudraCT number; outcome. There will be the possibility for some customisation, storing customised queries and reports; hyperlinks to case folders in database, and options to select output formats.

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